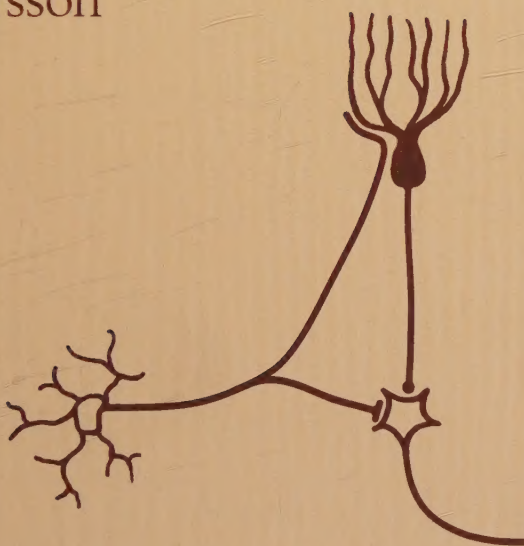


Functional Organisation of Climbing Fibre Input to Sagittal Compartments in the Cerebellum

By
Gert Andersson



Lund 1982

FUNCTIONAL ORGANISATION OF CLIMBING FIBRE INPUT
TO SAGITTAL COMPARTMENTS IN THE CEREBELLUM

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Title and subtitle FUNCTIONAL ORGANISATION OF CLIMBING FIBRE INPUT TO SAGITTAL COMPARTMENTS IN THE CEREBELLUM			
Abstract The functional organisation of the climbing fibre input to the sagittal zones in the cerebellar anterior lobe and to the lateral vestibular nucleus (LVN) was studied in the cat. In the LVN, the majority of neurones are inhibited by Purkinje cells in the b zone in the cerebellar vermis. These LVN neurones are also activated by collaterals of the climbing fibres to the b zone. These findings support the identification of the cerebellar functional unit with the sagittal compartment consisting of a sagittal zone of cerebellar cortex and its associated cerebellar or vestibular nucleus. There is a somatotopic organisation in the peripheral climbing fibre input to the b zone which is divided into narrow (100-200 um) sagittal microzones. The most lateral microzone receives an input from the tail and hindlimbs. More medial microzones receive inputs from successively more rostral body segments (trunk, forelimbs and face). The input is bilateral. Three different spino-olivocerebellar pathways converge onto the b zone. Each microzone in the b zone projects to a separate group of LVN neurones, which also receive collaterals only from climbing fibres ascending to that microzone. It is proposed that a microzone and its associated nuclear neurones represent the basic computational unit in the cerebellum. Each zone receives two or more climbing fibre paths from the cerebral cortex. The climbing fibre paths have different origins and characteristics. All zones receive their predominant projection from the motor cortex (posterior sigmoid gyrus). The c2 zone receives, in addition, a particularly strong projection from the second somatosensory area and the d1 zone from the anterior sigmoid gyrus and the parietal cortex. There is a topographical organisation in the cortico-olivocerebellar projection. Furthermore, the a, b, c2 and d1 zones, which receive a bilateral peripheral input, receive a bilateral cortical input, whereas the x, c1 and c3 zones, which receive an ipsilateral peripheral input only, receive a strictly contralateral cortical input.			
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*Cats and monkeys, monkeys and cats -
all human life is there.*

Henry James (1843-1916)

(in *The Madonna of the Future*)

To Norma

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This thesis is based on the following articles which will be referred to by their Roman numerals:

- I. Projections to lateral vestibular nucleus from cerebellar climbing fiber zones. Exp. Brain Res. 32, 549-564 (1978). With O. Oscarsson.
- II. Climbing fiber microzones in cerebellar vermis and their projection to different groups of cells in the lateral vestibular nucleus. Exp. Brain Res. 32, 565-579 (1978). With O. Oscarsson.
- III. Spinal, trigeminal and cortical climbing fibre paths to the lateral vermis of the cerebellar anterior lobe in the cat. Exp. Brain Res. 44, 71-81 (1981). With L. Eriksson.
- IV. Origin and sagittal termination areas of cerebro-cerebellar climbing fibre paths. (1982). Manuscript. With J. Nyquist.

INTRODUCTION

The function of the climbing fibre system in the cerebellum is still largely unknown despite much scientific interest. A number of theories have, however, been proposed. These have approached the question of climbing fibre function along two lines:

1. How are the synaptic connections between the climbing fibres and their target neurones arranged and what is the synaptic action of the climbing fibres on these neurones?
2. What information is carried by the climbing fibres?

It is now generally accepted that the inferior olive is the main, if not the exclusive, source of climbing fibres (Szentágothai and Rajkovits 1959; Eccles, Ito and Szentágothai 1967; Desclin 1974; Batini, Corvisier, Destombes, Gionni and Everett 1976; Montarolo, Raschi and Strata 1980). This unique anatomical arrangement has made it possible to stimulate the climbing fibres selectively and to study their effects on the cerebellar neurones. For a detailed description of the neuronal circuitry of the cerebellar cortex and the synaptic actions of the two major input systems, the mossy and climbing fibres, the reader is referred to the monograph of Eccles et al. (1967).

With reference to the present study, it should be noted that the climbing fibres exert a powerful synaptic action on the Purkinje cells, evoking responses which have been called "complex spikes" (Thach 1967). These responses have a very low discharge rate of approximately 1/sec, which should be compared to the background activity of the "simple spikes" of the Purkinje cells at 30 - 60 Hz (Granit and Phillips 1956; Eccles et al. 1967; Thach 1968). Thus, the climbing fibres do not seem to be primarily concerned with the instantaneous control of the Purkinje cell discharge rate. The simple spike discharge is, presumably, largely generated by activity in the parallel fibres.

It has been suggested that the climbing fibre impulses modify the parallel fibre - Purkinje cell synapses in such a way as to increase (Marr 1969) or decrease (Albus 1971) the synaptic efficacy. This plasticity might be a mechanism for motor learning in the cerebellum. The observations of Gilbert and Thach (1977) that Purkinje cells display an increased complex spike frequency and a decreased simple spike frequency during motor learning favour the proposal of Albus (1971). The climbing fibres

also appear to induce plastic changes in the flocculus during adaptation of the vestibulo-ocular reflex (Ito 1980). Recently, it has been shown that climbing fibre activation of Purkinje cells reduces the efficacy of simultaneously activated parallel fibre synapses on the same Purkinje cells, while parallel fibres which are not active at the same time have an unaltered effect on the Purkinje cells (Ito, Sakurai and Tongroach 1982). The mechanism which mediates this effect might be a prolonged plateau-like depolarisation of the Purkinje cell dendrites produced by climbing fibre activation (Ekerot and Oscarsson 1981). This plateau may be generated by an inward calcium current (Llinás and Sugimori 1980).

With regard to the problem of the information carried by the climbing fibres, another question arises : Is there a division of the cerebellum such that individual areas receive functionally different information and send their efferent signals through separate channels?

A longitudinal division of the cerebellum into functional regions was first demonstrated by Chambers and Sprague (1955a, b) who reported that lesions and stimulation in three zones, vermis, pars intermedia and pars lateralis, produce different motor effects. These findings were related to the anatomical study by Jansen and Brodal (1940), which had shown that the cerebellar cortex is divided into three longitudinal zones, with different cortico-nuclear projections.

Since then, a number of investigations have revealed a more detailed organisation of the cerebellum. A study of the myeloarchitecture of the white matter demonstrated a division of the cerebellum into sagittally organised compartments, each containing one band of thicker fibres and one band of thinner fibres (Voogd 1964, 1969). Each compartment, with a width of about one mm, contains the Purkinje cell axons from a sagittal zone of cortex projecting to the intracerebellar or vestibular nucleus (or part of nucleus) associated with that zone (Voogd 1969; Voogd and Bigaré 1980). In addition, it was demonstrated that each compartment receives climbing fibres from a restricted part of the inferior olive (Voogd 1969; Groenewegen and Voogd 1977; Groenewegen, Voogd and Freedman 1979). These studies have been confirmed by other anatomical investigations (for references see Brodal 1980; Brodal and Kawamura 1980; Courville and Faraco-Cantin 1980; Walberg 1980). In addition, in good agreement with the anatomical findings, Armstrong, Harvey and Schild (1974) demonstrated a zonal organisation in the olivo-cerebellar projection using electro -

physiological methods.

A series of physiological investigations have demonstrated that the spino-olivo-cerebellar pathways, ascending through different funiculi in the spinal cord, terminate in sagittally oriented zones in the cerebellar cortex of the anterior lobe and paramedian lobule (Oscarsson and Uddenberg 1966; Oscarsson 1968, 1969; Larson, Miller and Oscarsson 1969a, b; Armstrong, Harvey and Schild 1973a; Oscarsson and Sjölund 1977a, b; Ekerot and Larson 1979a). These zones are defined by their receptive fields and by the latencies of the climbing fibre responses on peripheral nerve stimulation and, additionally, appear to be identical with the zones described by Voogd (see above).

The mossy fibre - parallel fibre input to the cerebellum might span several zones, since the parallel fibres run perpendicularly to the zones and have a length of up to 5 - 7 mm (Brand, Dahl and Mugnaini 1976), which far exceeds the width of the zones. However, there is a longitudinal organisation in the mossy fibre input to the cerebellar cortex in at least some of the mossy fibre systems, as shown for the exteroceptive component of the cuneo-cerebellar tract (Ekerot and Larson 1980).

The findings on the olivo-cerebellar and cortico-nuclear projections show that the cerebellar compartments, each consisting of a sagittal zone and its associated intracerebellar or vestibular nucleus (or part of a nucleus), receive different climbing fibre inputs and, through their efferent connections, reach different motor systems. It has been suggested that these compartments constitute the functional units of the cerebellum, each controlling a particular motor mechanism (Oscarsson 1973, 1980).

In order to test the hypothesis that each zone is a functional unit, having a private climbing fibre input and access to a separate efferent channel, the experiments described in papers I and II were performed. The organisation of the olivo-cortical, olivo-nuclear and cortico-nuclear projections was studied at the single neurone level in one well-defined compartment comprising the b zone and the lateral vestibular nucleus (LVN). The results were in agreement with the functional unit hypothesis and, additionally, showed that the b zone is divided into microzones, which project to separate groups of LVN neurones.

Concerning the question of what information is carried by the climbing fibres, many theories have been advanced (for detailed discussion see Armstrong 1974; Eccles 1977). One hypothesis is of particular interest

for the present study: the error signal hypothesis, which is based on studies on the vestibulo-ocular and opto-kinetic reflexes. This hypothesis suggests that the climbing fibres convey signals about errors in oculomotor performance and introduce plastic changes in the flocculus (see above; Ito 1972, 1980; Barmack and Hess 1980a, b; Barmack and Simpson 1980). The error detected by the inferior olive is a slip of the retinal image when, for example, the eye movements do not compensate adequately for head rotation. This hypothesis gains support from the findings that the complex spike activity of floccular Purkinje cells is modulated during adaptation of the vestibulo-ocular reflex (Ito 1980).

When considering the movements of the body and the limbs, the error signalling function becomes more complicated, since a large range of movements can be performed. These movements are subject to varying external loads and perturbations. What would then be considered as an error must be based on a comparison between the intended and the performed movement. This is considered in the comparator hypothesis (Miller and Oscarsson 1970; Oscarsson 1980) which suggests that the inferior olive acts as a comparator of convergent descending and ascending inputs. The descending pathways would carry information about motor command signals and the ascending pathways about the activity induced by these signals in lower motor centres and the resulting movement. When there is a mismatch between the command signals and the ascending information, the inferior olive would send an error signal to the cerebellum.

A prerequisite for the comparator hypothesis is that the inferior olive neurones receive input from higher motor centres (e.g. cerebral cortex) and from lower motor centres in the brainstem and spinal cord and/or from the periphery. Although many studies have been dedicated to the cortico-olivo-cerebellar projection (Provini, Redman and Strata 1968; Miller, Nezlina and Oscarsson 1969; Allen, Azzena and Ohno 1974a, b; Miles and Wiesendanger 1975a, b; Sasaki, Oka, Matsuda, Shimono and Mizuno 1975; Oka, Yasuda, Jinnai and Yoneda 1976; Rowe 1977; Oka, Jinnai and Yamamoto 1979), they have not been concerned with the possible differential input to the functional units of the cerebellum, i.e. the sagittal compartments. Therefore, the latter part of this study was dedicated to the zonal organisation in the cortico-olivo-cerebellar projection (III; IV).

METHODOLOGICAL CONSIDERATIONS

The experiments were performed on young, adult cats anaesthetised with pentobarbitone or alpha-chloralose. Some cats, initially under pentobarbitone anaesthesia, were decerebrated and received no further anaesthetics. Detailed methodological descriptions are given in the separate papers. Only some general comments will be made here.

In the experiments of papers I - III, the spinal cord was transected at the level of the third cervical segment sparing only one or two of the ventral, dorsal and dorsolateral funiculi. Thus, the peripheral input through the ventral (VF-, Oscarsson and Sjölund 1977a), dorsal (DF-, Ekerot and Larson 1979a) and dorsolateral (DLF-, Larson et al. 1969a) spino-olivo-cerebellar pathways (SOCs) could be identified. In papers I and II, the isolation of the ventral funiculus permitted a study of the VF-SOC input to the b zone and the LVN, isolated from other pathways. This was a prerequisite for the analysis which was performed (see below, Results).

Peripheral nerves were stimulated with a high stimulus strength (20 times the nerve threshold) which was supramaximal for evoking climbing fibre responses. The cerebral cortex was stimulated either with silver ball electrodes on the surface or with a needle electrode, insulated except for the tip, inserted to a depth of 2 mm. Microelectrode recordings of neurones in the lateral vestibular nucleus and of single Purkinje cells were also obtained. The locations of microelectrode tracks and recording sites were assessed from values read off the micromanipulator during the experiments and from reconstructions based on histological sections. The cerebellar lobules were identified according to Larsell (1953).

RESULTS AND COMMENTS

A. Identification of the Cerebellar Functional Unit

If the sagittal compartments, described above, are the functional units of the cerebellum, each compartment must receive a private input and must, also, have access to a separate efferent channel through which it controls that particular motor mechanism with which the compartment is concerned (Oscarsson 1973). In order to test this hypothesis, the connections between the inferior olive, the cerebellar cortex and the lateral vestibular nucleus (LVN) were studied (I). Three questions were posed:

1. Which of the sagittal zones in the hemivermis project to the LVN?
2. Do Purkinje cells from more than one zone project to the same LVN neurones?
3. Are the LVN neurones excited exclusively by the collaterals of that climbing fibre path which projects to the sagittal zone supplying the inhibition?

The experiments were performed on cats with the spinal cord transected, sparing only the right ventral funiculus. Thus, the ventral spino-olivo-cerebellar paths (VF-SOCs) were isolated and the climbing fibre mediated responses to limb nerve stimulation could be identified with respect to the sagittal zones (Oscarsson and Sjölund 1977a, b). Simultaneous recordings were made of the climbing fibre responses in the cerebellar zones and of the synaptic potentials in the LVN neurones on limb nerve stimulation (I, Fig. 1).

The inferior olive has a dual influence on the LVN neurones: monosynaptic excitation through collaterals of climbing fibres and disynaptic inhibition through climbing fibre activated Purkinje cells (Ito and Yoshida 1966; Ito, Obata and Ochi 1966). The LVN cells were classified as aCF or bCF neurones based on the similarity between the receptive fields and latencies of the synaptic potentials in these neurones and the receptive fields and latencies of the climbing fibre (CF) responses evoked in the Purkinje cells of either the a or b zone. Five percent of the LVN cells were classified as aCF, and 75% as bCF neurones. The remaining neurones did not receive any direct (excitatory) or indirect (inhibitory, through Purkinje cells) input from the climbing fibres (I, Table 1; see also Ito, Kawai and Udo 1968; Allen, Sabah and Toyama 1972). No LVN neurones displayed response characteristics

similar to those of the Purkinje cells in the c1 zone, located adjacent to the b zone in the extreme lateral part of the vermis and the medial part of the pars intermedia (Oscarsson and Sjölund 1977a).

All bCF neurones had bilateral receptive fields. Some were influenced from the hindlimb nerves, some from the forelimb nerves and some from both hindlimb and forelimb nerves. The dominating response was an IPSP which was usually preceded by an EPSP. In each cell, the EPSP was only evoked from those nerves which also evoked an IPSP. This suggests that a certain group of LVN neurones and the Purkinje cells inhibiting them are innervated by branches of the same climbing fibres.

Stimulation of the cerebellar surface provided additional data for classification of the climbing fibre influenced LVN neurones (cf Ito et al. 1968). With such stimulation in the b zone, the bCF neurones displayed a short-latency, monosynaptic IPSP (cf Ito and Yoshida 1966) followed by a late IPSP (4-5 ms; I, Fig. 4). The late IPSPs were presumably produced by activating climbing fibres which, through branching in the sagittal plane (Faber and Murphy 1969; Armstrong, Harvey and Schild 1973b, c; Oscarsson and Sjölund 1977b), activated additional Purkinje cells in the b zone which projected to the LVN neurones studied. Usually, the late IPSPs were preceded by late EPSPs which were presumably mediated by climbing fibre collaterals to the LVN neurones.

The aCF neurones were mainly influenced from the ipsilateral hindlimb nerve (I, Fig. 5), corresponding to the climbing fibre input to the a zone (Oscarsson and Sjölund 1977a). Cerebellar surface stimulation was only effective in eliciting IPSPs in aCF neurones from the stimulus electrode in the a zone.

Thus, it was demonstrated that there exist two groups of LVN cells which are inhibited from Purkinje cells in the a and b zones, respectively. Although they were intermingled in the LVN (I, Fig. 6), their synaptic inputs were completely separate. Calculations based on these data and those given by Palkovits, Magyar and Szentágothai (1971) and by Palkovits, Mezey, Hámori and Szentágothai (1977) suggest that most, if not all, Purkinje cells in the b zone project to the LVN.

The existence of a projection from the b zone to the LVN has been confirmed by anatomical studies in which horseradish peroxidase (HRP) injections were made in the LVN (Corvaja and Pompeiano 1979; Voogd and Bigaré 1980) as well as by a physiological study in which recordings from

LVN neurones were made on electrical stimulation of the cerebellar vermis (Fanardjian and Sarkissian 1980).

The results in paper I suggest that each cerebellar zone has, in addition to a specific climbing fibre input, its own efferent path(s) through which its control of the appropriate motor function can be mediated, as proposed by Oscarsson (1973). Thus, it is likely that a sagittal compartment, consisting of a cortical zone and its associated nuclear neurones, constitutes the functional unit of the cerebellum.

B. Organisation of Fibre Connections in the Sagittal Compartment

On the assumption that the sagittal zones and their associated nuclei are the functional units of the cerebellum, another question arises: Does the whole unit participate in the computation of a particular motor task or are there subdivisions which represent the basic computational units?

In order to answer this question, a detailed study of the organisation in the b compartment was performed. Firstly, the somatotopic organisation in the climbing fibre input to the b zone through the VF-SOCP was studied. Thereafter, the observed somatotopic pattern was compared to the characteristics of the responses in the LVN neurones on limb nerve stimulation.

Recording the responses of single Purkinje cells in the b zone on stimulation of limb nerves demonstrated a distinct somatotopy in the climbing fibre projection to this zone (II, Fig. 1). Based on the input characteristics to the Purkinje cells, the b zone was divided into five microzones. The most lateral microzone received input exclusively from the hindlimbs (II, Fig. 2A, B, C). More medially, followed a microzone in which the cells received a strong synaptic input from both hindlimb nerves and a weak, and late, input from the forelimb nerves (II, Fig. 2D). The adjacent microzone contained cells which received a short-latency and equally strong synaptic input from, usually, all four limb nerves (II, Fig. 2E). Further medially, the Purkinje cells were activated with a short latency from the forelimb nerves and with a longer latency from the hindlimb nerves (II, Fig. 2F). In the most medial microzone, the Purkinje cells were exclusively activated from the forelimb nerves (II, Fig. 2G).

Further observations on the peripheral input to the b zone indicate that this zone can be divided into an even larger number of microzones, if the input from the tail, trunk and face is considered (III, Figs. 1 and 4). However, it should be emphasised that there are no sharp borders between the microzones. There is, rather, a gradual change of the input characteristics across the b zone.

On the basis of their receptive fields, the bCF neurones in the LVN were divided into three groups which received synaptic inputs from the nerves of the hindlimbs, forelimbs and all four limbs, respectively (II, Fig. 3). The hindlimb bCF neurones must receive inhibition exclusively from the Purkinje cells in the lateral microzone with only hindlimb input and the forelimb bCF units from the most medial microzone with an exclusive forelimb input. The bCF neurones with a mixed input, having an early IPSP on hindlimb nerve stimulation and a late IPSP on forelimb stimulation presumably received a projection only from the microzone with early hindlimb and late forelimb input (cf II, Fig. 5). Similarly, the few cells found with an early IPSP on forelimb nerve stimulation and late IPSP on hindlimb nerve stimulation should receive a projection from the microzone with early forelimb and late hindlimb input. Correspondingly, it is likely that the LVN neurones with early IPSPs on both hindlimb and forelimb nerve stimulation were inhibited from the microzone with equal hindlimb and forelimb input.

The conspicuous parallelism in the size and occurrence of the EPSPs and IPSPs evoked by the climbing fibre path in the same LVN neurones (see above) suggests that the LVN neurones receive excitation mediated mainly, or exclusively, by collaterals of those climbing fibres which activate the Purkinje cells supplying the inhibition.

A vague somatotopical organisation of the LVN has been reported by many investigators (Wilson 1972; Brodal 1974; ten Bruggencate, Teichmann and Weller 1975; ten Bruggencate, Scherer and Teichmann 1975; Fanardjian and Sarkissian 1980) and was confirmed in this study. Thus, despite the intermingling of the different groups of bCF neurones in the LVN, there is a high degree of specificity in the fibre connections in the b compartment. The Purkinje cells in one microzone receive an input from a small group of inferior olive neurones and project to a private group of LVN neurones. These latter receive collateral input from the climbing fibres projecting to the microzone which supplies the inhibition. These findings suggest that

the microzone and its associated nuclear neurones represents the basic computational unit in the cerebellum. It can, however, not be excluded that the basic computational units are smaller than described in the present study.

C. Convergence of Spinal Climbing Fibre Paths to the b Compartment

According to the comparator hypothesis, the spino-olivary pathways carry information about the activity in lower motor centres and/or about performed movements (Miller and Oscarsson 1970). Since each zone receives convergent climbing fibre inputs through more than one SOCP (for references see Ekerot and Larson 1979a; Oscarsson 1980), it is likely that they convey different but complementary information about the motor function with which the compartment is concerned. Thus, a knowledge of the pathways projecting to a compartment and what information is carried is necessary for the understanding of the function of that compartment. Following the description of the intrinsic organisation in the b compartment, a study of the convergence of climbing fibre pathways to the b zone was performed (III).

In a study on the DF-SOCP, Oscarsson (1969) described a strip in the most lateral part of the vermis receiving ipsilateral hindlimb input and, more medially, a strip restricted to the caudal vermis which receives ipsilateral forelimb input. It was previously assumed that these termination areas overlapped the termination areas of the VF-SOCP in the vermis (Oscarsson and Sjölund 1977a). In order to determine if the projection areas of these two pathways overlap, or are parts of separate zones, climbing fibre responses on limb nerve stimulation were recorded in the lateral vermis in preparations with spinal cord lesions leaving both the dorsal and ventral funiculi intact. Thus, the projection through the VF- and DF-SOCPs could be studied simultaneously.

Stimulation of the ipsilateral sciatic nerve evoked responses restricted to one sagittal strip in the lateral b zone. Since climbing fibre responses from this nerve are mediated through both the VF- and DF-SOCPs, this demonstrates that the hindlimb components of these two pathways converge onto the lateral part of the b zone.

The responses evoked on ipsilateral ulnar nerve stimulation could be ascribed to either the VF- or DF-SOCP according to their latencies

(Oscarsson and Sjölund 1977a; Ekerot and Larson 1979a; III, Fig. 2). It was demonstrated that the DF-SOCP mediated forelimb responses were evoked medial to those mediated through the VF-SOCP (III, Fig. 3). When the responses of single Purkinje cells were recorded, it was found that these two pathways terminated in two non-overlapping areas (III, Fig. 4). In addition, it was demonstrated that the DF-SOCP termination zone received collaterals of the climbing fibres to the c1 zone in the pars intermedia and paramedian lobule (III, Figs. 3, 5). This has later been confirmed by Ekerot and Larson (1982). These findings seem to justify the identification of the forelimb DF-SOCP termination area as a separate zone, which has been denoted the x zone (Ekerot and Larson 1979a).

Furthermore, it was demonstrated that the b zone receives a projection also through the DLF-SOCP (III, Fig. 5). Thus, the lateral part of the b zone receives a convergent input through three SOCPs, the DF-, DLF- and VF-SOCPs, while the medial part receives input through only two SOCPs, lacking input through the DF-SOCP. This difference between the hindlimb and forelimb components of the b compartment must have a functional meaning which, however, is unknown. It is interesting to note that there are differences in the convergence patterns between the forelimb and hindlimb parts of other zones too (see Ekerot and Larson 1979a).

D. Climbing Fibre Input to the Cerebellar Compartments from the Cerebral Cortex

According to the comparator hypothesis (Miller and Oscarsson 1970; Oscarsson 1980), the descending climbing fibre pathways to a compartment carry information about command signals to the lower motor centre with which the compartment is concerned. For a better understanding of the function of the compartment, this descending input must be specified. Therefore, the cortico-olivo-cerebellar projection to the sagittal zones in the cerebellar anterior lobe (with the exception of the d2 zone) was investigated. This study was carried out on pentobarbitone- or chloralose-anaesthetised cats in which the cerebral cortex was stimulated and the evoked climbing fibre responses were recorded in the cerebellar zones, defined by their peripheral inputs (III; IV).

Climbing fibre responses were evoked on stimulation of several areas in the cerebral cortex (IV, Figs. 2, 3, 4). The dominating climbing fibre

input to the cerebellar zones originates in the pericruciate cortex (IV, Figs. 3, 8). In all zones except d1, the responses evoked on stimulation of the posterior sigmoid gyrus (PSG) were larger and had lower thresholds and shorter latencies than the responses evoked from other cortical areas.

Two non-overlapping areas in the PSG project to the pars intermedia zones (c1, c2, c3 and d1). The lateral area projects to the caudal (forelimb) parts of the zones and the medial PSG area projects to the rostral (hindlimb) parts of the zones (IV, Figs. 5, 6A). In contrast, the b zone receives a projection from only one PSG area. Most of the minimum threshold sites for evoking responses in the b zone were centred between the two PSG areas projecting to the pars intermedia zones (IV, Fig. 6B). In the projection to the b zone, there is also a topographical organisation such that stimulation of the lateral part of the area evokes responses in the medial (forelimb) part of the b zone and stimulation of successively more medial parts of the PSG evokes responses in successively more lateral parts of the b zone (IV, Fig. 4).

The d1 zone was characterised by a short-latency input from a large area in the anterior sigmoid gyrus (ASG, IV, Figs. 3, 7). The responses evoked from the ASG in the d1 zone had thresholds which were as low as, or lower than, the responses evoked from the PSG. Stimulation of the lateral ASG evoked long-latency responses in the other zones (IV, Figs. 3, 5, 6). These responses were probably due to the activation of a slower conducting cortico-olivo-cerebellar pathway than that originating in the PSG.

From the first and second somatosensory areas, SI and SII (see Jones and Powell 1973), climbing fibre responses were also evoked, albeit with higher thresholds and longer latencies than the responses from the PSG (IV, Figs. 2, 3, 4). There was a topographical organisation in this projection. The forelimb areas of SI and SII projected to the forelimb parts of the cerebellar zones (IV, Figs. 2, 4). Stimulation of the face receiving area of the coronal gyrus evoked climbing fibre responses in those parts of the b, c2 and c3 zones which also receive a trigeminal climbing fibre input (IV, Figs. 3, 4, 8). Also, the d1 zone, in which climbing fibre responses were evoked only occasionally on trigeminal nerve stimulation, received an input from the coronal gyrus.

The SII differed from the SI in that climbing fibre responses could

be evoked more readily. This applied especially to the c2 zone in which responses were evoked from the SII with nearly as low thresholds and short latencies as those from the PSG (IV, Fig. 3).

Stimulation of the parietal cortex (rostral parts of the lateral and suprasylvian gyri) regularly evoked responses in the d1 zone, but less frequently in other zones (IV, Figs. 2, 3). The thresholds for evoking responses in the d1 zone were usually as low as those from the PSG and ASG, while higher strengths were required, in most cases, to evoke responses in the other zones.

The a, b, c2 and d1 zones which, to a varying extent, receive a bilateral peripheral climbing fibre input (Larson et al. 1969; Oscarsson and Sjölund 1977a; IV), also receive a bilateral cortical input. The x, c1 and c3 zones which receive only an ipsilateral peripheral input (Ekerot and Larson 1979a), receive a strictly contralateral cortical input (IV, Fig. 8).

Thus topographically organised climbing fibre projections from several areas in the cerebral cortex to all zones studied in the cerebellar anterior lobe were demonstrated. These projections are, presumably, mediated through a multitude of cortico-olivo-cerebellar pathways. In addition to confirming previous reports (Provini et al. 1968; Miller et al. 1969; Allen et al. 1974a, b; Miles and Wiesendanger 1975a, b; Sasaki et al. 1975; Oka et al. 1976; Rowe 1977), the findings reported in papers III and IV demonstrate a specificity in the cerebral climbing fibre projection to the sagittal zones.

GENERAL DISCUSSION

A. Identification of the Cerebellar Functional Unit

It is now well documented that the cerebellar cortex is divided into sagittal zones which can be identified by their climbing fibre inputs (Oscarsson 1973; Groenewegen and Voogd 1977; Oscarsson and Sjölund 1977a, b; Ekerot and Larson 1979a, Groenewegen et al. 1979). Each cortical zone has access to a separate efferent channel, consisting of a pool of nuclear neurones (I; II; Voogd and Bigaré 1980), which in turn project to a motor centre. The nuclear neurones also receive collateral excitation from the climbing fibre path to the cortical zone supplying inhibition to the neurones. These findings strongly suggest that a cerebellar compartment, consisting of a cortical zone and its associated intracerebellar (or vestibular) nuclear neurones, constitutes the functional unit of the cerebellum (Oscarsson 1973). Each compartment would control a particular motor mechanism. The climbing fibre paths projecting to a compartment would monitor activity within this mechanism.

B. Identification of the Basic Computational Unit

Each compartment is presumably divided into subunits. These may be concerned with the control of different motor tasks performed by that particular compartment. These subunits probably constitute the basic computational units of the cerebellum (II). The cortical representation of such a computational unit would be the microzone, receiving a well-defined input and projecting to a private group of nuclear neurones. Such an organisation has been demonstrated for the b compartment in which the microzones receive a somatotopically organised input (II). Experimental evidence, discussed below, strongly suggests that a similar organisation also exists in other compartments.

Ekerot and Larson (1979b, 1980) have demonstrated a detailed topographical organisation of both mossy and climbing fibre inputs to the c3 zone in the pars intermedia. The projection areas of ipsilateral forelimb nerves constitute narrow strips which might be the equivalents of the microzones in the b zone. There are, however, some differences. Thus, the microzones in the b zone are oriented in a strictly sagittal

direction and extend throughout the whole zone, or a considerable part of it (II). The strips in the c3 zone deviate partly from the sagittal orientation of the zone and have a relatively limited longitudinal extent (Ekerot and Larson 1979b). Furthermore, there are no distinct borders between the microzones in the b zone, while the borders between the strips in the c3 zone seem to be sharper. The differences in the organisation of the climbing fibre input to the b and c3 compartments may reflect differences in function.

The b compartment controls the activity of extensor motoneurons through the lateral vestibulo-spinal tract (Ito et al. 1968; Lund and Pompeiano 1968; Grillner and Hongo 1972; I; II). Each computational unit may control the activity in extensor motoneurons along a part of the neuraxis. This activity would be essential for maintaining the posture and would not be discretely localised to only one or a few muscles. The bilateral, widely convergent inputs to single Purkinje cells (II, Fig. 1; III, Fig. 4) ensure integration of information about the activity in several segments. Similarly, the branching of vestibulo-spinal axons to both cervical and lumbar segments (Abzug, Maeda, Peterson and Wilson 1974) and the bilateral effects of the vestibulo-spinal tract on spinal motoneurons (Hongo, Kudo and Tanaka 1975) are suitable arrangements for the coordination of extensor muscle activity bilaterally in several segments.

The detailed somatotopical organisation of the climbing fibre input to the c3 zone (Ekerot and Larson 1979b), on the other hand, suggests that the c3 compartment is concerned with some aspects of motor control which requires a high degree of spatial discrimination. It has been demonstrated that microstimulation in the interpositus nucleus elicits contractions of single muscles or groups of related muscles (Asanuma and Hunsperger 1975). These effects are mediated through the interposito-rubro-spinal pathway. Additionally, microstimulation of the afferent fibres to the intermediate cerebellum in the brachium pontis (Perciavalle, Santangelo, Sapienza, Savoca and Urbano 1977, 1978) and in the restiform body (Perciavalle, Santangelo, Sapienza, Serapide and Urbano 1978) elicits contractions in single muscles. It seems likely that such a microstimulation activates a pool of interpositus neurons which constitute the efferent pathway of a computational unit. Therefore, it may be suggested that a cortical strip in the c3 zone, receiving a very restricted peripheral input (Ekerot and Larson 1979b),

together with a pool of interpositus neurones, activating a single muscle (or a group of functionally related muscles), constitute the basic computational unit in the c3 compartment.

C. Functional Significance of Afferent Connections to the Sagittal Compartment

The cerebellar anterior lobe has often been referred to as the spino-cerebellum. This is, however, somewhat misleading. In the present study, the climbing fibre responses evoked on stimulation of the cerebral cortex were, in all zones, as large as those from the periphery. As discussed below, the convergence and interaction of descending and ascending climbing fibre inputs to the anterior lobe are presumably of crucial importance to its function. It should be emphasised that this convergence and interaction occur already at the olivary level or perhaps, in some cases, at a preolivary level (cf. Miller et al. 1969).

As demonstrated in papers III and IV, there is a remarkable parallelism in the cerebral and peripheral climbing fibre inputs to the compartments in the cerebellar anterior lobe. Thus, there is a convergence of multiple paths both from the cerebral cortex and from the spinal cord to each olivary region projecting to a cerebellar compartment. Moreover, the cerebral and spinal inputs to each olivary region and corresponding compartment match with respect to somatotopy and uni- or bilaterality.

These findings are consistent with the comparator hypothesis (Miller and Oscarsson 1970; Oscarsson 1980) according to which the olive evaluates the correctness of motor acts by comparing motor commands from higher centres with the activity these commands induce in lower motor centres, and with the resulting movement. The relevant information would be carried by the paths to the olive from the cerebral cortex and spinal cord. It would be expected, as was actually found, that the descending and ascending paths related to the same cerebellar compartment have a number of characteristics in common.

Whereas identification of the target neurones of the efferent channel provide clues to what motor function is controlled by the compartment, identification of the information carried by the descending and ascending climbing fibre paths to the compartment will be crucial for an understanding of the computations performed by the functional unit in the cerebellum.

SUMMARY

1. The functional organisation of the climbing fibre input to the sagittal zones in the cerebellar anterior lobe and to the lateral vestibular nucleus (LVN) was studied in the cat.
2. In the LVN, the majority of the neurones are inhibited by Purkinje cells in the b zone in the cerebellar vermis. These LVN neurones are also activated by collaterals of the climbing fibres to the b zone.
3. These findings support the identification of the cerebellar functional unit with the sagittal compartment consisting of a sagittal zone of cerebellar cortex and its associated cerebellar or vestibular nucleus.
4. There is a somatotopic organisation in the peripheral climbing fibre input to the b zone which is divided into narrow (100-200 μm) sagittal microzones. The most lateral microzone receives an input from the tail and hindlimbs. More medial microzones receive inputs from successively more rostral body segments (trunk, forelimbs and face). The input is bilateral. Three different spino-olivo-cerebellar pathways converge onto the b zone.
5. Each microzone in the b zone projects to a separate group of LVN neurones, which also receive collaterals only from climbing fibres ascending to that microzone.
6. It is proposed that a microzone and its associated nuclear neurones represent the basic computational unit in the cerebellum.
7. Each zone receives two or more climbing fibre paths from the cerebral cortex. The climbing fibre paths have different origins and characteristics.
8. All zones receive their predominant projection from the motor cortex (posterior sigmoid gyrus). The c2 zone receives, in addition, a particularly strong projection from the second somatosensory area and the d1 zone from the anterior sigmoid gyrus and the parietal cortex.
9. There is a topographical organisation in the cortico-olivo-cerebellar projection such that forelimb parts of motor and sensory cortices project to the forelimb parts of the zones and hindlimb cortical areas project to the hindlimb parts of the zones. Furthermore, the a, b, c2 and d1 zones, which receive a bilateral peripheral input, receive a bilateral cortical input, whereas the x, c1 and c3 zones, which receive an ipsilateral peripheral input only, receive a strictly contralateral cortical input.

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ORIGIN AND SAGITTAL TERMINATION AREAS OF CEREBRO-CEREBELLAR
CLIMBING FIBRE PATHS

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SUMMARY

Climbing fibre responses were recorded in the cerebellar anterior lobe on stimulation of the cerebral cortex. A zonal pattern was demonstrated in the cortical projection, which was related to the cerebellar sagittal zones, as identified from peripheral climbing fibre input. In all zones, except c2, a covariation of the responses evoked on peripheral nerve stimulation and on stimulation of the corresponding part of the sensori-motor cortex was found.

There was a bilateral projection to the a, b, c2 and d1 zones which also, to a varying extent, receive a bilateral peripheral input. The x, c1 and c3 zones, receiving an ipsilateral peripheral input, were activated exclusively from the contralateral cortex.

Stimulation of the posterior sigmoid gyrus (PSG) evoked responses in all the zones. These responses had, in all zones except d1, lower thresholds and shorter latencies than the responses from other cortical areas.

Two separate PSG areas were shown to project to the pars intermedia zones (c1, c2, c3, d1); the lateral area to the caudal parts and the medial area to the rostral parts of the zones. In contrast, the b zone received a projection from only one PSG area, centred between, but overlapping, the two areas projecting to the pars intermedia zones.

Stimulation of the anterior sigmoid gyrus (ASG) evoked short-latency responses in the d1 zone and long-latency responses in all other zones.

Stimulation of the first and second somatosensory areas (SI and SII) was generally less effective in evoking climbing fibre responses than was stimulation of the PSG. The only exception was the c2 zone, in which responses were evoked from the SII with nearly as low thresholds and short latencies as on PSG stimulation.

From the parietal cortex, long-latency responses were regularly evoked in the d1 zone and less frequently in the a, b and c2 zones.

Key words: Cerebellum - Climbing fibre zones - Cerebral cortex - Cortico-olivo-cerebellar pathways

INTRODUCTION

It is now generally accepted that the inferior olive is the major, if not exclusive, source of climbing fibres to the cerebellum (Szentágothai and Rajkovits 1959; Eccles et al. 1967; Armstrong 1974; Desclin 1974; Batini et al. 1976). The functional role of the olivo-cerebellar system is, however, still unknown despite many anatomical and physiological studies (for references see Eccles et al. 1967; Armstrong 1974; Brodal and Kawamura 1980; Ito 1980; Oscarsson 1980). It has been proposed that the climbing fibres convey signals about errors in motor performances (Barmack and Hess 1980; Barmack and Simpson 1980; Ito 1980). These error signals would induce plastic changes in the cerebellar cortex and result in improved performance (Marr 1969; Albus 1971; Ito 1980). It has been suggested that the errors are detected by the inferior olive acting as a comparator (Miller and Oscarsson 1970; Oscarsson 1980): the inferior olive receives information from descending pathways which mediate motor commands and from ascending pathways which monitor the ongoing activity in lower motor centres and the resulting movement. From a comparison of these converging inputs, the inferior olive might detect deviations from the intended movement and inform the cerebellum about these deviations.

The ascending paths, the spino-olivo-cerebellar paths (SOCs), have been thoroughly investigated with respect to their functional properties, as well as to their origin and course in the spinal cord and their termination areas in narrow sagittal strips in the cortex of the cerebellar anterior lobe (for references see Ekerot et al. 1979; Armstrong and Schild 1980; Oscarsson 1980).

The climbing fibre input to the cerebellum from the cerebral cortex has also been described in several reports (Provini et al. 1968; Miller et al. 1969a; Allen et al. 1974a,b; Miles and Wiesendanger 1975a, b; Sasaki et al. 1975; Oka et al. 1976, 1979; Rowe 1977a), as have the responses in the inferior olive to stimulation of the cerebral cortex (Armstrong and Harvey 1966; Crill and Kennedy 1967; Crill 1970). These studies showed a topographically organised convergence of peripheral and cortical climbing fibre inputs to the cerebellum, which is consistent with the comparator hypothesis. However, in these studies, the climbing fibre responses were not localised in relation to the sagittal zones which presumably constitute the functional units of the cerebellar cortex, each controlling a particular

motor mechanism (Oscarsson 1980). Nor were the cortical areas giving rise to the climbing fibre responses adequately delineated.

Therefore, the present study was conducted in order to investigate the cortico-olivo-cerebellar projection to each of the climbing fibre zones in the anterior lobe. Particular emphasis was laid on the projection from the pericruciate cortex to the forelimb parts of the zones. A preliminary report has been given (Andersson and Nyquist 1980).

METHODS

The experiments were performed on 30 adult cats (2.0-3.5 kg), 21 under pentobarbitone and 9 under chloralose anaesthesia. The latter were given supplementary doses (2-5 mg/kg) of pentobarbitone to suppress the mossy fibre responses. The animals were paralysed with gallamine triethiodide and artificially ventilated. The arterial blood pressure, end-expiratory CO_2 concentration and rectal temperature were continuously monitored and kept within physiological limits.

The sciatic and ulnar nerves were dissected bilaterally and mounted for stimulation. In some experiments, the superficial and deep radial nerves were also stimulated. The infraorbital branches of the trigeminal nerves (henceforward referred to as trigeminal nerves) were stimulated bilaterally with needle electrodes inserted through the gingiva (Andersson and Eriksson 1981). All nerves were stimulated at 20 times nerve threshold.

Craniotomies were performed to expose the cerebellar anterior lobe on the left side and the cerebral pericruciate cortex bilaterally. In many cases, the cerebral exposure was extended to include other cortical areas such as the parietal cortex and the first and second somatosensory areas. Photographs were taken of the cerebellar and cerebral surface and the exposed parts were then covered with warm mineral oil to prevent drying. Climbing fibre responses were recorded, with silver ball electrodes, as positive field potentials at the surface. In some experiments, the activity of single Purkinje cells was recorded with glass micropipettes filled with a 3M KCl solution and having a resistance of 3-6 M Ω .

The cerebral cortex was stimulated either at the surface with monopolar silver ball electrodes or at a depth of 2 mm with a needle electrode, insulated except for the tip and having a resistance of 10-20 k Ω . The

cortex was stimulated cathodally with 1-5 square pulses of 200 μ s duration using a constant current stimulator. The train frequency was 300-400 Hz and the stimuli were applied 1-2 times per second. The maximal stimulus intensities employed were 3 mA for surface stimulation and, with the exception of the experiment illustrated in Fig. 1, 1.5 mA for intracortical stimulation. Prior to cortical stimulation, the responses on peripheral nerve stimulation were recorded at the stimulation site on the surface of the cerebral cortex.

RESULTS

I. Functional Properties of Cortico-Cerebellar Pathways

The cortico-olivo-cerebellar projection was studied by recording climbing fibre responses evoked in the cerebellum on stimulation of the cerebral cortex. Fig. 1A shows records of responses recorded, under pentobarbitone anaesthesia, from the cerebellar surface on stimulation of the contralateral cerebral cortex with different stimulus intensities and number of shocks. The cortex was stimulated cathodally with a monopolar needle electrode at a depth of 2 mm. The evoked responses consisted of two components: a short-latency (3 ms), slowly rising positivity due to synaptic activation of granule cells by a mossy fibre input and a second, steeply rising positivity at 13-16 ms due to a climbing fibre activation of Purkinje cells (Eccles et al. 1967, 1968; Armstrong and Harvey 1968; Provini et al. 1968; Allen et al. 1972, 1974a).

In most preparations under barbiturate anaesthesia, the mossy fibre responses were considerably smaller than illustrated here. Under chloralose anaesthesia, they were large and almost concealed the climbing fibre responses. Since the aim of the present study was to investigate the latter, small amounts of pentobarbitone were given in these cases in order to depress the mossy fibre responses. Under such circumstances, it has been proposed that the amplitude of the climbing fibre responses is increased (Gordon et al. 1973; Allen et al. 1979). Additionally, pentobarbitone stabilised the climbing fibre responses which fluctuate heavily under chloralose anaesthesia (Oscarsson and Sjölund 1977).

With a high stimulus strength (e.g. 1.2 mA), the climbing fibre response

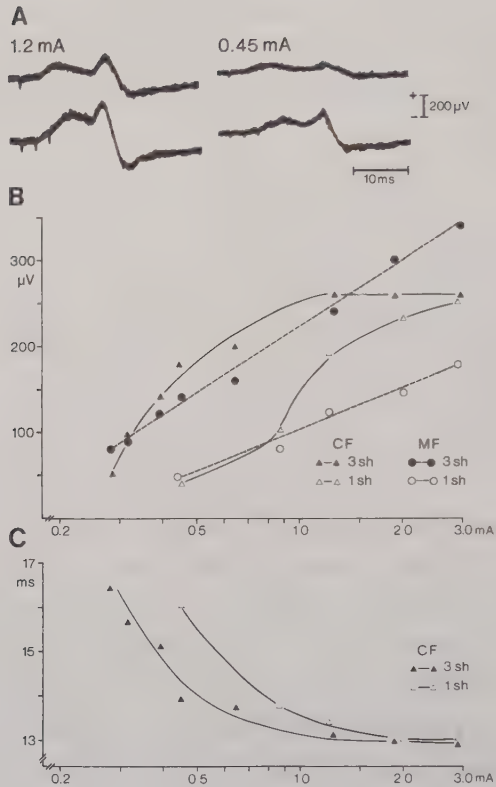


Fig. 1. Characteristics of mossy and climbing fibre responses to cerebral intracortical stimulation.

A. Responses recorded at the cerebellar surface to stimulation of the contralateral posterior sigmoid gyrus with an intracortical needle electrode. A single shock (sh) and a train of three shocks were used with varying intensities. Positivity in this, and all other Figures, upwards.

B. Relation between stimulus strength and the amplitudes of climbing fibre (CF) and mossy fibre (MF) responses.

C. Relation between stimulus strength and climbing fibre response latencies. Pentobarbitone anaesthesia.

to stimulation of the cortex with one or three shocks was essentially the same (Fig. 1A). In some cases, as in the example illustrated in Fig. 1, the climbing fibre responses evoked with two shocks were similar to those evoked with three shocks. In other cases, stimulation with three shocks evoked climbing fibre responses with slightly lower thresholds and larger amplitudes than those evoked with two shocks. An increase in the number of shocks above three did not reduce the threshold further nor increase the amplitudes. Therefore, stimulation with three shocks was regularly employed.

When using lower stimulus intensities (e.g. 0.45 mA, Fig. 1A), there was a clear difference between responses evoked with one and with three shocks. This is further illustrated in Fig. 1B and C. In B, the mossy fibre and climbing fibre response amplitudes are plotted against the stimulation strengths. The climbing fibre responses evoked with a single shock were much smaller than those evoked with three shocks at low stimulation strengths. At higher stimulus intensities, the amplitudes did not grow further when the stimulus strength or the number of shocks was increased, implying a saturation of the cortico-olivo-cerebellar pathway. In contrast, the amplitudes of the mossy fibre responses (dashed lines) were increased both by increasing the stimulus strength and the number of stimuli at all strengths tested.

The latencies of the cortically evoked climbing fibre responses depended, to a large extent, on the stimulus intensities used (Fig. 1C). When the stimulus intensity was increased from threshold, there was a gradual decrease of the latencies, by several ms, to a plateau level, in this case 13 ms. Thereafter, further increase of the stimulation strength resulted in no, or only a very slight, decrease of the response latency. At low strengths, the response latency to a single shock was longer than that to double or triple shock stimulation.

In this study, the response latencies used for analysis (cf. Fig. 3) were measured from the first shock at stimulation strengths where a moderate increase in strength did not reduce the latency further, i.e., when the synaptic delays in the cortico-olivo-cerebellar pathways had become minimal. Usually, this plateau on the latency curve was reached between 0.5 and 1.0 mA with intracortical stimulation and between 1.0 and 2.5 mA with surface stimulation, if the stimulus electrode was optimally located.

II. Identification of Cortico-Olivo-Cerebellar Projections

The mapping of the climbing fibre input to the cerebellar anterior lobe from the cerebral cortex was achieved using two different strategies:

1. Ten to twenty stationary stimulus electrodes were placed at fixed sites on the cerebral surface, which were identified by the surface configuration (sulci and gyri) and the peripheral input (e.g., maximal responses in the first somatosensory area). A recording electrode was moved in small steps (0.3-1 mm) along the surface of a cerebellar folium. Peripheral nerves were stimulated in order to identify the cerebellar sagittal zones (Oscarsson 1973; Oscarsson and Sjölund 1977; Ekerot and Larson 1979a), and then the responses elicited from different cortical stimulation sites were studied. The amplitudes of the responses from peripheral nerves and cortical stimulation sites were plotted along the folium (see Fig. 2A), and the cortical input to each zone was specified.

2. Stationary recording electrodes were placed on the cerebellar surface. The recording sites were chosen so that each electrode recorded maximal responses evoked from the periphery in each of the studied zones. Either a silver ball electrode for surface stimulation or a needle electrode for intracortical stimulation was moved in small steps along the cerebral cortex. The responses evoked from peripheral nerves were recorded at each cortical stimulation site prior to stimulation of that site. Based on the results from this procedure, a map of the cerebral cortical area(s) projecting to a certain zone was constructed (see Fig. 5).

The first strategy permitted an analysis of the zonal organisation in the projection from any stimulation site. However, it was not possible to determine the borders of the cerebral cortical areas projecting to the cerebellum, nor to locate the minimum threshold sites. When a response was evoked from a certain site only with a rather high stimulus intensity, it was impossible to know whether the response was due to stimulus spread to an adjacent cortical area or to activation of a cortico-olivo-cerebellar pathway originating at the site, but requiring much spatial summation.

With the second strategy, it was possible to delineate the cerebral projecting areas as well as to identify the sites from where responses with minimal thresholds and latencies and maximal amplitudes were evoked. On the other hand, responses could be recorded from only a few sites in each cerebellar zone.

In most experiments, the recording session was begun with strategy 1, and when it had been determined in which zones the most favourable recordings could be made in that particular experiment, the second strategy was employed.

Fig. 2 shows an experiment in which the caudal folium of lobule Vc was mapped with a surface recording electrode. Fig. 2B is a map of the left cerebellar anterior lobe. The points and stars along the folium indicate the recording sites and the borders between the sagittal zones are indicated with dotted lines. Fig. 2C shows the cortical stimulation sites and the responses evoked at these sites on stimulation of the ulnar (upper traces) and sciatic (lower traces) nerves contralateral to the cortical sites.

In Fig. 2A, the amplitudes of the climbing fibre responses recorded from lobule Vc are plotted and the latencies indicated. To the right are records from the sites marked with stars. Responses in successively more lateral zones, identified from their peripheral inputs, will be described.

The a zone in the medial vermis receives a long-latency hindlimb input which is often bilateral (Oscarsson and Sjölund 1977). In the experiment illustrated in Fig. 2, no, or only small, responses were evoked in the lateral part of the zone on cerebral cortical stimulation. More medially, responses were evoked from nearly all stimulation sites. In fact, when the stimulation strength was 2 mA or more, responses were evoked from all ten stimulation sites.

The x zone, lateral to a, receives information from the ipsilateral forelimb and the short-latency response (16-17 ms) on ipsilateral ulnar nerve stimulation in the medial part of the b+x division in Fig. 2A can be ascribed to the activation of Purkinje cells in the x zone (Ekerot and Larson 1979a; Andersson and Eriksson 1981). When the x zone was as narrow as in Fig. 2A, it was impossible to separate it spatially from the medial part of the b zone when the responses were recorded only as surface potentials (Andersson and Eriksson 1981).

The b zone in the lateral vermis receives a bilateral input from the periphery. Caudal body segments project to the lateral part, and more rostral segments project to successively more medial parts (microzones) of the zone (Oscarsson and Sjölund 1977; Andersson and Oscarsson 1978; Andersson and Eriksson 1981). In the experiment illustrated in Fig. 2, responses were evoked in the lateral part of the b zone from the medial PSG electrodes, bilaterally. Overlapping these responses but shifted

Fig. 2. Distribution of climbing fibre responses elicited in one folium on stimulation of peripheral nerves and cerebral cortex.

A. Distribution of climbing fibre responses along one folium in the cerebellum. Response latencies indicated. To the right, records of responses in four of the zones, recorded at the sites indicated with stars to the left and in B.

B. Left cerebellar anterior lobe, lobules IV-Vc (nomenclature of Larsell 1953). Dots and stars indicate recording sites.

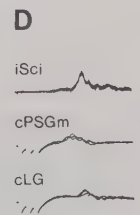
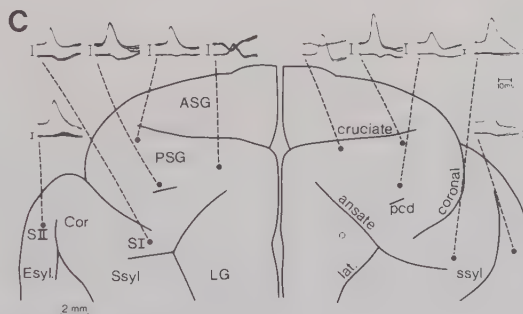
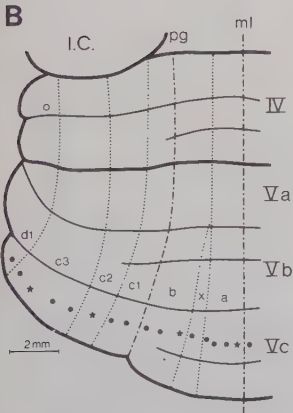
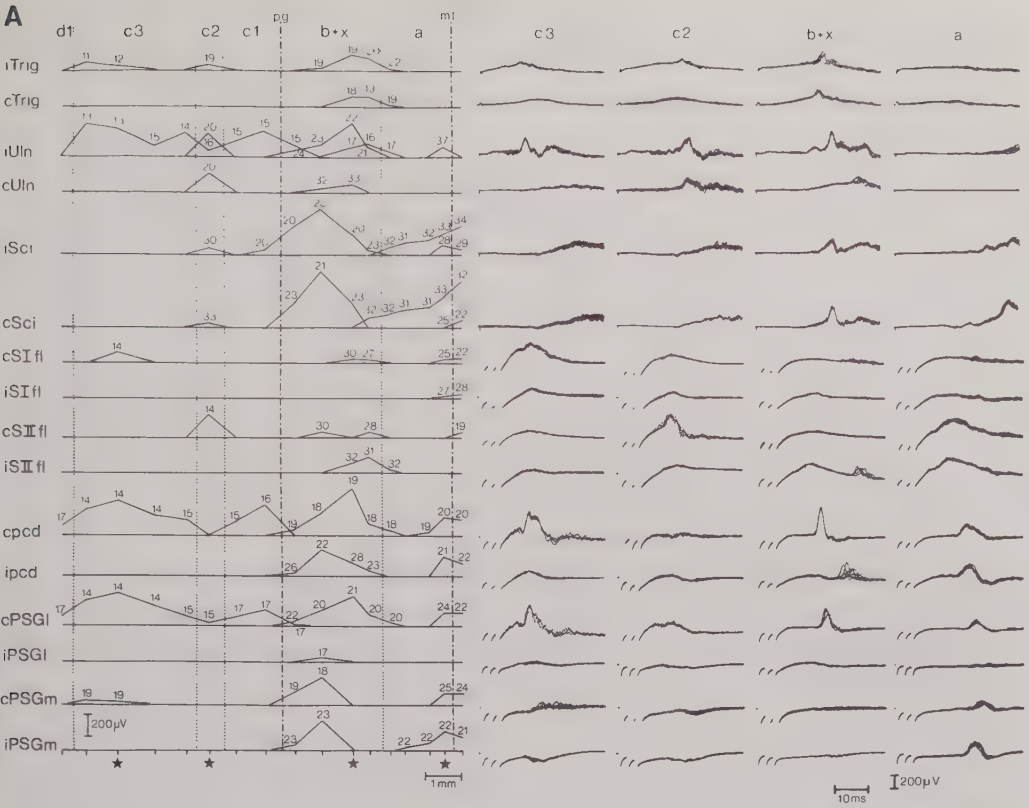
C. Cerebral cortex and stimulation sites (viewed from dorsal direction). At each site, records of responses evoked on contralateral ulnar nerve (upper traces) and sciatic nerve (lower traces) stimulation are shown. Vertical bars 200 μ V. Ring indicates stimulation site in the contralateral lateral gyrus. Names of gyri indicated to the left and names of sulci to the right, according to Hassler and Muhs-Clement (1964).

D. Records of responses evoked in the d1 zone in lobule IV (indicated with a ring in B).

Abbreviations: i ipsilateral; c contralateral; Trig trigeminal; Uln ulnar; Sci sciatic nerves; SI fl and SII fl forelimb areas of first and second somatosensory areas; pcd post-cruciate dimple; PSG posterior sigmoid gyrus; l lateral; m medial; ASG anterior sigmoid gyrus; Cor. coronal gyrus; Esyl ectosylvian gyrus; Ssyl suprasylvian gyrus; LG lateral gyrus; lat lateral sulcus; ssyl suprasylvian sulcus; pg paravermal groove; ml midline; I.C. inferior colliculus.

Cerebellar zones according to Oscarsson (1980).

Chloralose anaesthesia.



slightly medially, responses were recorded on stimulation of the forelimb parts of both posterior sigmoid gyri (contralateral and ipsilateral PSGl and pcd). Due to the difficulty in separating the responses in the medial b zone and the x zone, it was not possible to ascribe the responses from the SI and SII specifically to one of these zones. However, when the stimulation strength was increased to 2.5 mA, more laterally located responses of considerably larger amplitudes, with latencies of 22-25 ms, were evoked bilaterally from the SI and SII electrodes. This suggests that the responses were evoked in the b zone.

The c1 zone in the medial pars intermedia receives, in lobule Vc, ipsilateral forelimb input (Ekerot and Larson 1979a). In the illustrated experiment (Fig. 2A), responses were evoked on cortical stimulation only from the forelimb part of the contralateral PSG.

The c2 zone receives a long-latency input from all four limbs without a distinct somatotopy (Larson et al. 1969b; Ekerot and Larson 1979a). In addition, in the present investigation, responses were recorded on ipsilateral and, usually also, contralateral trigeminal nerve stimulation (latencies 15-22 and 18-28 ms, respectively). In the illustrated experiment (Fig. 2A), the forelimb site in the contralateral second somatosensory area (cSIIfl) was the only cortical site from which a climbing fibre response could be evoked in the c2 zone.

The c3 zone receives, in lobule V, a short-latency climbing fibre input mainly from the ipsilateral forelimb (Ekerot and Larson 1979a, b). In the present investigation, a short-latency response (9-12 ms) in a lateral strip in the c3 zone (in lobule Vc) was also frequently observed on stimulation of the ipsilateral trigeminal nerve. In the experiment of Fig. 2, short-latency responses (14 ms) were evoked mainly from the forelimb parts of the contralateral first somatosensory area (cSIfl) and posterior sigmoid gyrus (cPSGl and cpcd).

The d1 zone receives ipsilateral forelimb input in lobule V and ipsilateral hindlimb input in lobule IV and, to some extent, in lobule V (Larson et al. 1969a; Ekerot and Larson 1979a). In the present study, responses to contralateral limb nerve stimulation were also occasionally evoked (latencies 21-24 ms). In the experiment illustrated in Fig. 2, the d1 zone was very narrow in lobule Vc and no, or only very small, responses were recorded there. Recordings were also made from a folium in lobule IV in this experiment. Here the d1 zone was wider, and at the site indicated with a

circle in Fig. 2B, a large response from the ipsilateral sciatic nerve was evoked. In 2D, records are shown of responses evoked at this site. Of the cortical stimulation sites in C, only the medial one on the contralateral PSG (cPSGm) was effective in evoking a response (latency 15 ms). In addition, stimulation of the rostral part of the lateral gyrus, indicated with a circle in 2C, evoked a response at a latency of 19 ms. Stimulation of this site evoked no responses in lobule Vc.

The results presented in Fig. 2 demonstrate that climbing fibre responses can be evoked from several areas. The histograms in Fig. 3 show the response latencies to stimulation of the different areas in the contralateral and ipsilateral cortex, displayed above and below the abscissa, respectively. The values were obtained by selecting, in each experiment, the shortest response latency in each zone. The characteristics of the projections from each cortical area will be briefly described.

Stimulation of the Posterior Sigmoid Gyrus (PSG) evoked responses in all zones in nearly all experiments. In all zones, except d1, these responses had lower thresholds, larger amplitudes, and shorter latencies than the responses evoked from other cortical areas.

There was a topographical organisation in the projection from the PSG. Stimulation of the lateral part evoked responses in the x, medial part of the b, and caudal parts of the pars intermedia zones. In each zone except c2, these responses showed the same distribution pattern as that found on stimulation of large forelimb nerves (cf. Ekerot and Larson 1979a). Correspondingly, the medial part of the PSG projected to the a, the lateral part of the b, and the rostral parts of the pars intermedia zones, which are the main hindlimb receiving areas in the cerebellar anterior lobe (see below, section III).

Stimulation of the ipsilateral PSG was almost as effective as stimulation of the contralateral PSG in evoking responses in the a and b zones. Responses were less frequently seen in the c2 and d1 zones. In the zones receiving only ipsilateral peripheral input, small responses were observed only occasionally on stimulation of the ipsilateral PSG.

From a large area in the Anterior Sigmoid Gyrus (ASG), short-latency responses (12-13 ms) were evoked exclusively in the d1 zone (Fig. 3). These responses had as low, or lower, thresholds and as large amplitudes as those evoked from the PSG. Responses were also evoked in the d1 zone on ipsilateral ASG stimulation. These had approximately 5 ms longer

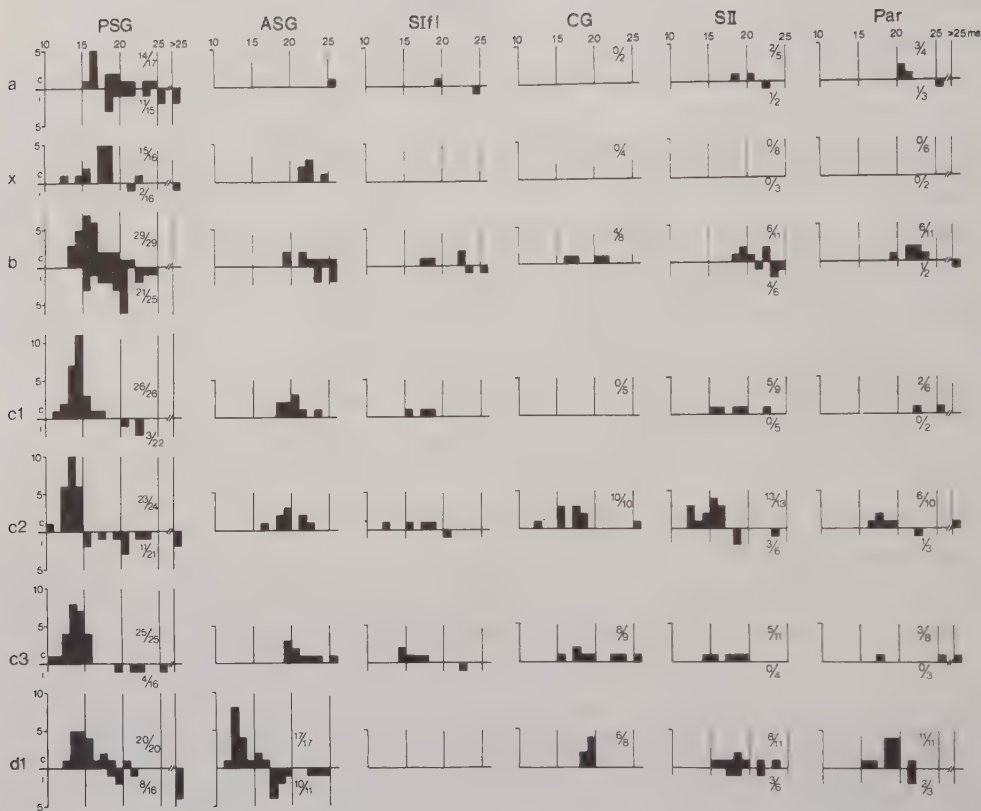


Fig. 3. Latencies of climbing fibre responses to stimulation of cerebral cortex. Contralateral (c) response latencies above, and ipsilateral (i) below the abscissa. In each experiment the shortest latency was selected for each zone. Numbers indicate in how many experiments responses were evoked in a certain zone out of the number of experiments tested for that particular projection. Abbreviations: PSG posterior sigmoid gyrus; ASG anterior sigmoid gyrus; SI fl forelimb area of first somatosensory area; CG coronal gyrus; SII second somatosensory area; Par parietal cortex.

latencies and 2-3 times higher thresholds than the contralaterally evoked responses.

In the other zones, responses were evoked only from the lateral part of the ASG. These responses had considerably longer latencies than those evoked from the PSG (Fig. 3). At least in the b zone (only zone tested), these long-latency responses were evoked also from the ipsilateral ASG.

The First Somatosensory Area (SI) was stimulated with a fixed stimulus electrode where maximal surface positive responses were evoked on forelimb nerve stimulation (Fig. 2). The climbing fibre responses evoked from SI occurred exclusively in the forelimb parts of the zones. The responses had higher thresholds and longer latencies than those evoked from the PSG (Fig. 3). In three experiments, intracortical stimulation was employed in the parts of SI with maximal responses on stimulation of the ulnar and superficial radial nerves. Climbing fibre responses were only evoked with stimulus strengths which were considerably higher than those required in the PSG.

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When fixed stimulus electrodes were used, it was not always possible to determine if the responses from the SI electrode were due to activation of the SI only, or to stimulus spread into the PSG area, particularly in those cases where the distance between the SI and PSG area was short and the threshold for evoking a response from the SI was considerably higher than that from the PSG area. Therefore, only the latencies of those responses that could be clearly ascribed to activation of the SI, i.e., if they had only slightly higher thresholds than the responses from the PSG, are included in Fig. 3 and only positive findings are considered.

On stimulation of the Coronal Gyrus at the site of maximal responses evoked on trigeminal nerve stimulation, climbing fibre responses were evoked in the b, c2, c3 and d1 zones. The latencies were usually 15-20 ms (Fig. 3). The responses were evoked in those parts of the zones receiving a trigeminal input. The occasional absence of responses in the b and c3 zones, indicated in the latency histograms in Fig. 3, reflects the inclusion of experiments in which recordings were made only from "non-trigeminal" parts of the zones.

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The d1 zone has not previously been reported to receive a trigeminal input. In the present study, climbing fibre responses were evoked in the d1 zone on stimulation of the ipsilateral trigeminal nerve in 5 (of 25 tested) cats (latencies 17-24 ms).

The Second Somatosensory Area (SII) in the anterior ectosylvian gyrus (see Jones and Powell 1973) was stimulated in 13 cats. Climbing fibre responses were regularly evoked in the c2 zone and less frequently in the other zones (Figs. 2 and 3). In five experiments, the SII was systematically mapped with an intracortical stimulus electrode. The minimal thresholds for evoking responses in the c2 zone were nearly as low as those for evoking responses from the PSG. To evoke responses in the other zones from the SII, considerably higher strengths were required.

A topographical organisation was found such that the anterior, forelimb part of the SII projected to the medial part of the b zone and the caudal parts of the pars intermedia zones, while the caudal, hindlimb area projected to the lateral part of the b zone and the rostral parts of the pars intermedia zones. There was, however, a considerable overlap in the projecting areas. The minimum threshold sites were usually found in that part of the SII which received convergent fore- and hindlimb inputs.

In six cats, the ipsilateral SII was also stimulated. In the two pentobarbitone anaesthetised cats, no climbing fibre responses were evoked. In the four cats under chloralose anaesthesia, climbing fibre responses were observed in the b, c2 and d1 zones (Fig. 3).

On stimulation of the Parietal Cortex (anterior parts of the lateral and suprasylvian gyri), responses were evoked in the d1 zone in all cases tested (Figs. 2 and 3). In the other zones, responses were less frequently observed. The effective area extended caudally from the ansate sulcus for a distance of approximately 3 mm. The thresholds for evoking responses in the d1 zone were usually as low as those for evoking responses from the PSG and ASG. To evoke responses in the other zones, higher stimulus strengths were usually required (with the exception of the c2 zone in chloralose anaesthetised cats).

There was a topographical organisation in the projection from the parietal cortex to the d1 zone such that stimulation of the suprasylvian gyrus tended to evoke larger responses in the caudal (forelimb) part of the d1 zone and stimulation of the lateral gyrus evoked larger responses in the rostral (hindlimb) part of the zone.

The results presented above demonstrate a projection from several cortical areas. Stimulation of different cortical areas often evoked responses at the same cerebellar recording site. In order to test if there

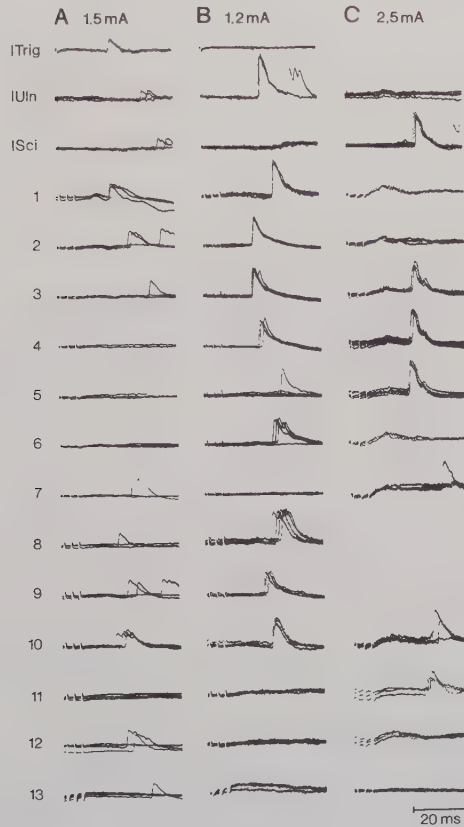
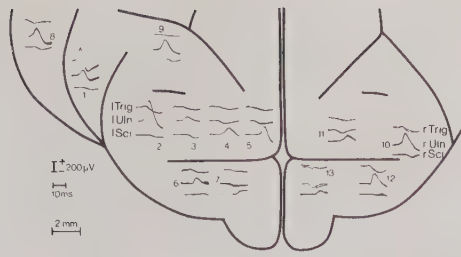


Fig. 4. Climbing fibre activation of single Purkinje cells (A, B and C) in the left b zone. Numbers in the cerebral map indicate positions of surface stimulus electrodes. Inlaid traces are responses at the stimulation sites evoked on stimulation of trigeminal (Trig), ulnar (Uln), and sciatic (Sci) nerves contralateral to the respective site. Cerebral stimulation strength indicated above the column of records from each cell. (Differences in amplitudes of cell A responses due to deterioration of the cell. Cell C lost before the series of recordings was finished). Chloralose anaesthesia.

was a convergence of the paths from several cortical areas also at a unitary level, recordings from single Purkinje cells were obtained (cf. Rowe 1977a). Fig. 4 shows records from three Purkinje cells encountered in successively more lateral microzones (Andersson and Oscarsson 1978; Andersson and Eriksson 1981) in the b zone in one experiment. The map of the cerebral cortex (viewed from a rostral direction) shows the positions of the stimulus electrodes and the responses evoked at each of these sites on stimulation of the trigeminal (upper trace), ulnar (middle trace), and sciatic (lower trace) nerves contralateral to the respective sites.

The three cells were identified as trigeminal (A), forelimb (B), and hindlimb (C) cells from their dominant peripheral inputs. The cells were activated on bilateral nerve stimulation, but only records of the ipsilateral nerve responses are shown. The trigeminal cell (A) was activated with the lowest threshold (0.6 mA) and shortest latency (18 ms) from the contralateral coronal gyrus (position 1). The cell was also activated from the lateral parts of the PSG on both sides but with higher thresholds and longer latencies (note that the cell was also activated from the limb nerves but with long latencies).

The forelimb cell (B) was activated from most of the sites. The shortest latency (16 ms) and lowest threshold (0.5 mA) was obtained from position 3. The threshold for evoking a response from the SI (site 9) was 0.7 mA and from SII (site 8) 1.2 mA. The response from the ipsilateral PSG (site 10) had a threshold of 1.0 mA.

The hindlimb cell (C) was activated from the medial parts of the PSG on both sides.

Thus, the cells received convergent inputs from several cortical areas. In addition, there was a topographical organisation in the projection to these cells with matching peripheral and cortical inputs. In two experiments, recordings were made from 45 Purkinje cells in the b, c1, c2 and d1 zones. With few exceptions, they all received convergent inputs from more than one cortical area. The cortical input also corresponded to the peripheral input.

III. Functional Organisation of Climbing Fibre Projection from the Pericruciate Cortex

The pericruciate cortex was the most effective cortical area in evoking

climbing fibre responses. Therefore, the projection to the cerebellar anterior lobe from the pericruciate cortex was investigated more systematically.

The projection from the pericruciate cortex to the c1 zone will be described in detail. In most respects, the description of this projection to the caudal (forelimb) part of the c1 zone also applies to the projection from the pericruciate cortex to the x zone and to the caudal parts of the c2, c3 and d1 zones. Likewise, the projection to the rostral (hindlimb) part of the c1 zone is similar to the projection to the rostral parts of the c2, c3 and d1 zones.

Fig. 5A is a map of the right pericruciate cortex (viewed from a rostral direction) in which records of responses evoked in the left caudal c1 zone are shown at those sites from where the responses were evoked (upper traces). The cerebral cortex was stimulated with an intracortical electrode (stimulation strength 1.0 mA). Before the electrode was inserted into the cortex, the responses evoked on left ulnar nerve stimulation were recorded from the surface (lower records). The dots and stars indicate the stimulation sites and, additionally, a latency of 15 ms. The traces shown in the upper right corner are the responses recorded in the left caudal (forelimb) c1 zone on stimulation of some ipsilateral peripheral nerves before (upper) and after (lower) cerebral mapping. There was a small decrease of the response amplitudes but no change of latencies during the experiment.

Responses could be evoked in the c1 zone from an area in the PSG between the postcruciate dimple and the lateral tip of the cruciate sulcus and, further rostrally, from the ASG. From the central sites of the area in the PSG, large, short-latency (15 ms) responses were evoked. When stimulating away from this central area, gradually smaller responses with longer latencies were evoked.

Fig. 5B shows the thresholds for evoking responses from the sites along the row indicated with arrows in A. Centrally, there was an area with thresholds at or below 250 μ A. When moving out from this central area, the thresholds increased steeply to values well above 500 μ A. In other experiments, similar observations were made. Therefore, a threshold of 500 μ A, or less, was used as the criterion of a cortico-olivo-cerebellar projection from a stimulation site.

The interrupted line in Fig. 5A encircles the area from which responses

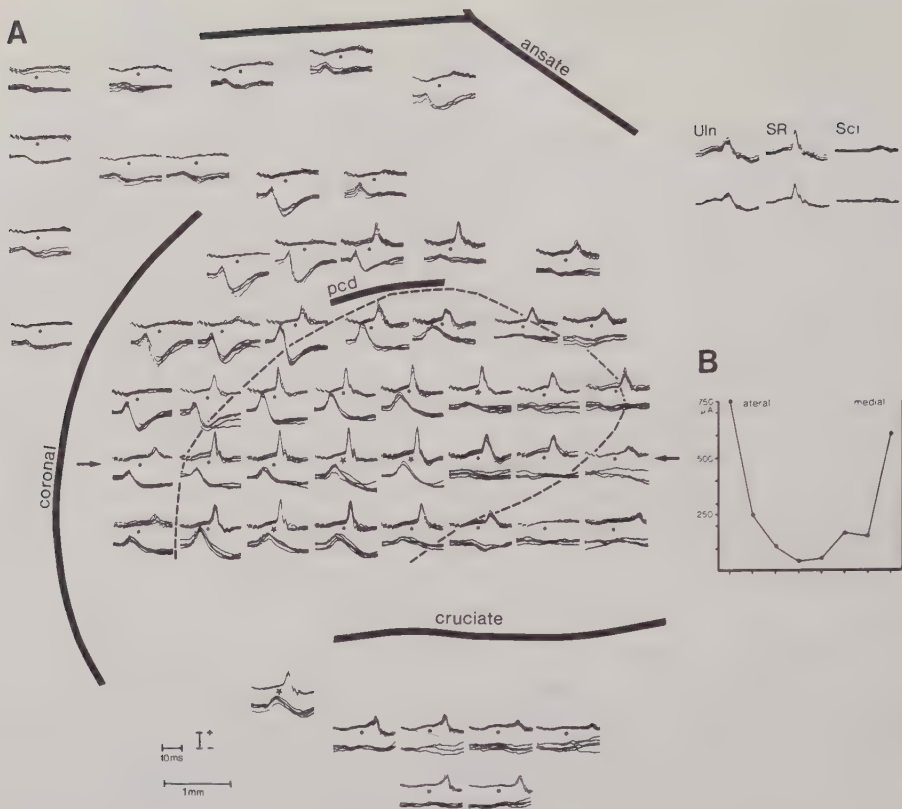


Fig. 5. Climbing fibre projection to the caudal c1 zone from the pericruciate cortex.

A. Map of the right pericruciate cortex. Dots and stars indicate stimulus sites and latency of 15 ms. Upper traces: responses in the left c1 zone to intracortical stimulation at depth of 2 mm (1 mA, 3 shocks). Lower traces: surface responses evoked at the site on stimulation of the left ulnar nerve. Interrupted line encloses area from which c1 responses could be evoked with stimulus strengths below 0.5 mA. Stars indicate sites with thresholds less than 100 μ A. Upper right: responses in the c1 zone to stimulation of left ulnar (l Uln), superficial radial (l SR), and sciatic (l Sci), nerves before (upper traces) and after (lower traces) mapping of the cerebral cortex. Vertical bar: 200 μ V for cerebellar responses and 100 μ V for responses in cerebral cortex.

B. Stimulus thresholds for evoking climbing fibre responses in the c1 zone from the row of stimulus sites indicated with two arrows in A. Pentobarbitone anaesthesia.

were evoked with a stimulus strength of 500 μ A or less. The responses from the ASG sites all had thresholds below 500 μ A. The stars indicate the sites where the thresholds were less than 100 μ A (in fact, all had thresholds of about 50 μ A). They were distributed in a crescent-shaped strip stretching from midway between the dimple and the lateral tip of the cruciate sulcus to an area rostralateral to the lateral tip of the cruciate sulcus.

The response latencies in the c1 zone were 15-17 ms from the whole area within the interrupted line. The responses evoked from the ASG had longer latencies (21-23 ms), with the exception of the response from the lateral-most point which had a latency of 17 ms. This suggests that this site belonged to the same functional area as the one in the PSG which henceforth will be referred to as the short-latency area. The long latencies of the responses from the other ASG sites indicate that these responses were due to activation of a slower conducting cortico-olivo-cerebellar pathway (see below).

It was a general finding that the short-latency projecting area was shifted medially relative to the areas receiving input from the ulnar and superficial radial nerves (cf. Fig. 5A). Usually, the lateral half of the projecting area overlapped the medial half of the area receiving input from the two forelimb nerves.

In some cats, the short-latency projecting area extended to behind the dimple. In four experiments, the deep radial nerve was stimulated in order to identify the area receiving group Ia input (Oscarsson and Rosén 1963, 1966). In all these cats the group I area lay 1-1.5 mm caudal to the cortical site with the lowest threshold for evoking climbing fibre responses in the forelimb zones. The lowest thresholds for evoking a response from group I receiving sites were 2-3 times higher than the minimum thresholds for evoking a response from the short-latency area. Climbing fibre responses evoked from group I sites were observed in all zones but a, which was not investigated.

Fig. 6A shows the minimum threshold sites for evoking short-latency responses in the caudal (forelimb, dots) part of the c1 zone in those experiments in which the pericruciate cortex was systematically mapped. The lowest thresholds for evoking short-latency climbing fibre responses in the caudal c1 zone were found within two areas. The caudal area lay midway between the lateral tip of the cruciate sulcus and the postcruciate dimple and the rostral area at the lateral tip of the cruciate sulcus

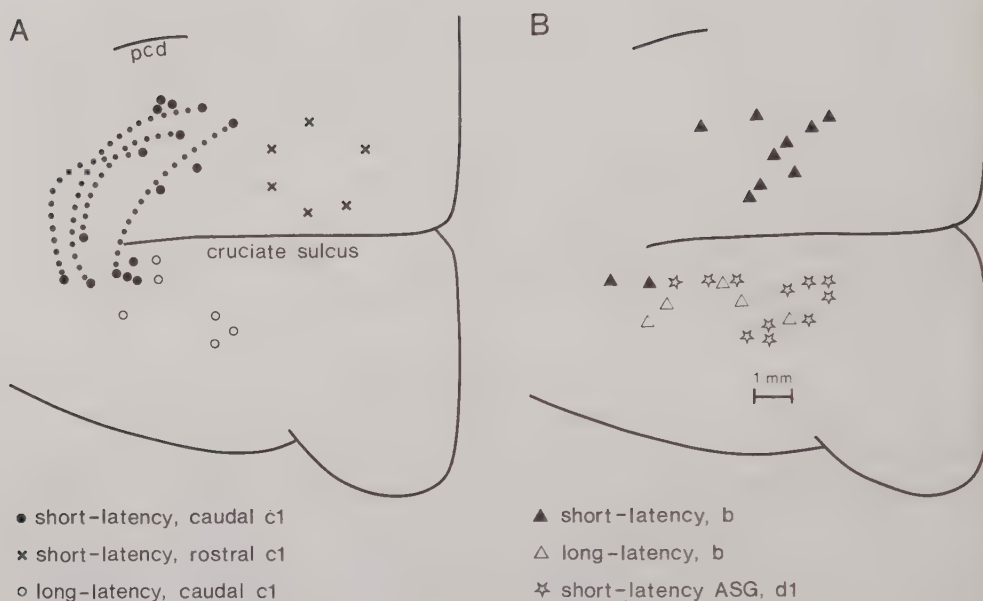


Fig. 6. Minimum threshold sites for evoking climbing fibre responses in the c1 (A) and b and d1 (B) zones.

Filled circles and crosses in A indicate the minimum threshold sites in the short-latency area for caudal and rostral parts of the c1 zone, respectively; filled triangles in B for the b zone. Dotted lines connecting two filled circles indicate strip of cortex with equally low thresholds. Unfilled circles (A) and triangles (B) indicate the minimum threshold sites in the long-latency ASG area for the caudal c1 and the b zone, respectively. Stars in (B) indicate the minimum threshold sites in the ASG short-latency area for the d1 zone.

pcd: post-cruciate dimple.

(within 2 mm in a lateral or rostral direction). In some cats, only one of these two areas could be distinguished. In other cats, both areas were observed, either as two separate areas or (as in Fig. 5A) as a strip of cortex extending from the caudal to the rostral area (indicated with dotted line in Fig. 6A).

The minimum threshold sites did not always coincide with the minimum latency and maximum amplitude sites. The optimal sites of these different parameters were often separated by one or a few mm. No systematic pattern in these differences was found.

The rostral (hindlimb) part of the c1 zone received a short-latency projection from an area in the medial PSG (Fig. 6A, crosses). The medial area projecting to the rostral c1 never overlapped the area projecting to the caudal c1. The lateral border of the medial area lay 4-7 mm lateral to the midline. In most experiments, the area extended rostrally to the cruciate sulcus and caudally to the level of the dimple. In each experiment, the minimum threshold site lay 4-5 mm medial to the corresponding site for the caudal c1 zone.

The minimum threshold sites for the rostral c1 zone sometimes coincided with the area receiving maximal sciatic input, but more often it was found slightly lateral to this area.

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The response latencies in the rostral c1 zone on stimulation of the medial PSG were usually 1-3 ms longer than those in the caudal c1 zone on stimulation of the lateral short-latency area. The difficulty in exposing the most medial part of the PSG and thus finding, and stimulating, the optimal hindlimb site could account for part of this difference. However, in those five experiments in which the minimum latency sites for both the caudal and rostral c1 were identified when mapping the PSG, the shortest response latencies in the rostral c1 zone on medial PSG stimulation were 0.5- 4ms (mean 1.5 ms) longer than the shortest response latencies in the caudal c1 zone on stimulation of the lateral short-latency area.

In seven experiments, long-latency responses (17-27 ms) were evoked in the rostral parts of the c1 and c3 zones on stimulation of the lateral short-latency area in the contralateral PSG. The response latencies were 4-13 ms (mean 6.5 ms) longer than the response latencies in the caudal parts of the zones evoked from the same area. In four cats, long-latency responses were evoked in the caudal parts of the c1 and c3 zones on medial PSG stimulation. The response latencies were 18-20 ms, i.e., 3-6 ms (mean

4.5 ms) longer than the response latencies in the rostral parts of the zones. These long-latency responses always had higher thresholds than the short-latency responses from the same area and were not studied further.

The results illustrated in Figs. 5 and 6A apply to the x, c1, c2 and c3 zones and also to the d1 zone (with the exception of the projection from the ASG, see below). In the experiment illustrated in Fig. 5, for example, recordings were also made in the x zone and the caudal parts of the c2 and d1 zones. These zones received a projection from the same cortical area as that projecting to the caudal c1 zone. The minimum threshold sites corresponded exactly for the c1 and c2 zones, while for the x and d1 zones, only the caudalmost site, indicated with a star, had a distinctly lower threshold than all the other sites.

In some experiments, small differences were observed between the areas projecting to the x and pars intermedia zones with respect to the borders and the minimum threshold sites. There were, however, no systematic differences, except that the x and d1 zones received a projection from a slightly smaller area. This might be correlated with the fact that the responses in these two zones often had higher thresholds than in the other zones.

Contrary to the vague somatotopy in the peripheral projection to the c2 zone (Larson et al. 1969b; Ekerot and Larson 1979a), the projection from the pericruciate cortex showed a distinct, topographical organisation. Thus, the medial short-latency area projected to the c2 zone in lobule Va and further rostrally. The lateral short-latency area projected to the entire lobule V and further caudally (at least to the rostral folium in lobule VI). Between these two projecting areas was a strip of cortex, 1-2 mm wide, from which responses could usually not be evoked with moderate stimulus strengths (0.5 mA, intracortical stimulation) in the c2 zone.

In contrast to the zones in the pars intermedia which received a projection from two short-latency areas, the b zone received a projection from only one area. In Fig. 6B, the minimum threshold sites for evoking short-latency responses in the b zone are shown (filled triangles). Most of the optimal sites were found in an area in the PSG located between the minimum threshold sites for the caudal and rostral parts of the c1 zone (cf. Fig. 6A). There was a topographical organisation such that the minimum threshold sites for evoking short-latency climbing fibre responses in the medial (forelimb) part of the b zone lay laterally in the PSG and

and in the ASG close to the lateral tip of the cruciate sulcus, whereas the minimum threshold sites for evoking responses in more lateral parts of the b zone lay successively more medial in the PSG (but not in the ASG). This is further illustrated in Fig. 4: the optimal site in the PSG for activating the forelimb cell (B) was site 3 and for the hindlimb cell (C) site 5.

The other Purkinje cells encountered in the b zone in this experiment showed the same pattern. The optimal cortical stimulation sites were position 1 for trigeminal cells, 2 and 3 for forelimb cells, 3 for cells with a dominant forelimb and weak hindlimb input, 3 and 4 for cells with equal forelimb and hindlimb inputs, and 4 and 5 for hindlimb cells. For comparison, the cells recorded in the caudal parts of the c1 and c2 zones in this experiment were all activated with the shortest latency from position 2, i.e., slightly lateral to the optimal site for the b zone forelimb cells.

The responses from peripheral nerves in the a zone are usually suppressed by barbiturate anaesthesia (Oscarsson and Sjölund 1977) and the cortical projection to this zone was studied in only a few experiments. In those two experiments in which the area in the PSG projecting to the a zone was mapped with an intracortical stimulus electrode, the projecting area was shifted slightly laterally to the area projecting to the hindlimb part of the c1 zone and overlapped, almost completely, the area projecting to the lateral part of the b zone. Stimulation of the sciatic nerve evoked no responses in the PSG area projecting to the a zone. Sciatic nerve responses were found more medially.

In experiments with stationary stimulus electrodes, responses in the a zone were often evoked also from the lateral PSG site and the electrode just rostral to the dimple (see Fig. 2). In these experiments long-latency responses from forelimb nerves were often seen in the a zone.

The areas in the ipsilateral PSG projecting to the a, b, c2 and d1 zones were homologous to the contralateral areas. The thresholds for evoking ipsilateral responses were usually 1.5-4 times higher than those for contralateral responses.

Responses evoked from the Anterior Sigmoid Gyrus (ASG) are illustrated in Fig. 5. Long-latency responses (20-22 ms) were evoked in the caudal c1 zone from all but the most lateral stimulation sites in the ASG. The response latencies were distinctly longer (average difference 5 ms) than

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those from the short-latency area. The thresholds for evoking these long-latency responses were rather low, 180-420 μ A. Thus, it is unlikely that they were due to stimulus spread into the short-latency area. In fact, the minimum threshold site for evoking a long-latency response was the medial of the two rostral sites, i.e., the site being most distant from the short-latency area.

Such long-latency responses were observed in the forelimb parts of all zones, except the d1 zone (see below), on stimulation of the lateral part of the ASG. The a zone was not investigated.

These observations suggest the existence of a cortico-olivo-cerebellar pathway originating in the ASG which has a slower conduction velocity and/or a greater number of intercalated neurones than the pathway from the short-latency area.

Fig. 6 (A and B) shows the minimum threshold sites for evoking long-latency responses in the forelimb parts of the c1 (circles) and b (unfilled triangles) zones, taken from those experiments in which the sites were identified on intracortical stimulation of the ASG. In some cases, there were small differences between the minimum threshold site locations for the different zones, but no systematic difference was found.

The minimum thresholds for evoking the long-latency responses from the ASG were usually 1.5-4 times higher than those for evoking short-latency responses. The area from which long-latency responses were evoked varied between the experiments from only one or two stimulation sites to an area covering several square mm.

It was a general finding that short-latency climbing fibre responses could be evoked in the cerebellum on stimulation of sites in the lateral ASG where ulnar nerve stimulation evoked responses at latencies of 7-9 ms (see Fig. 5A). At the sites from which long-latency climbing fibre responses were elicited, no, or only very small, surface positive potentials were evoked from the limb nerves in cats under pentobarbitone anaesthesia. Under chloralose anaesthesia, rather large responses with latencies of 20-25 ms were evoked from all four limbs in the ASG long-latency area.

The long-latency ASG area could not be identified in all experiments. When gradually more medial sites in the ASG were stimulated, a gradual increase in the climbing fibre response latencies, without a distinct low-threshold area, was observed in some cases. In other experiments, double responses were evoked from certain sites indicating that the pathways from

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both the short-latency and long-latency areas were activated simultaneously. In those cases, it was difficult to measure the latencies and amplitudes of the second response component.

In Fig. 3, the shortest latencies of the responses from the ASG long-latency area are selected from those experiments where long-latency responses could clearly be identified. Because of the abovementioned difficulties, only positive results are considered in Fig. 3.

Contrary to the other zones, the d1 zone received a short-latency climbing fibre input (12-13 ms) from the ASG (Fig. 3). These responses usually had lower thresholds and shorter latencies than those evoked from the PSG. Fig. 7 shows the responses in the left d1 zone in lobule IV from an experiment in which the right ASG was mapped with intracortical stimulation (stimulation strength 0.5 mA). Responses, with latencies of 13-15 ms, were evoked from a rather large area in the ASG. When the stimulation strength was increased to 1.0 mA, the response latency from most of the sites decreased to 12 ms. The minimum threshold for evoking a response was 150 μ A: the minimum threshold sites are indicated with stars. The response from the optimal site in the right (r) PSG was considerably smaller than from the ASG in this experiment. In other experiments, the response amplitudes on PSG stimulation were the same as or even larger than those on ASG stimulation.

The area from which short-latency responses could be evoked in the d1 zone often extended to at least 6 mm medially from the lateral tip of the cruciate sulcus. The ASG was seldom stimulated further medially. The locations of minimum threshold sites for the d1 zone, as identified in experiments with intracortical stimulation, are shown in Fig. 6B (stars). There was a large interexperimental variation in the spatial relation between the ASG area projecting to the d1 zone and the short-latency area and long-latency area projecting to the other zones. The area from which long-latency responses were evoked in the other zones usually overlapped the lateral half of the ASG area projecting to the d1 zone.

Responses were also evoked in the d1 zone on stimulation of the ipsilateral ASG. The stimulus strength required was usually 2-3 times higher than that required for evoking responses from the contralateral ASG. The ipsilateral response latencies were 17-19 ms, i.e., 5 ms longer than the contralateral ones (Fig. 3).

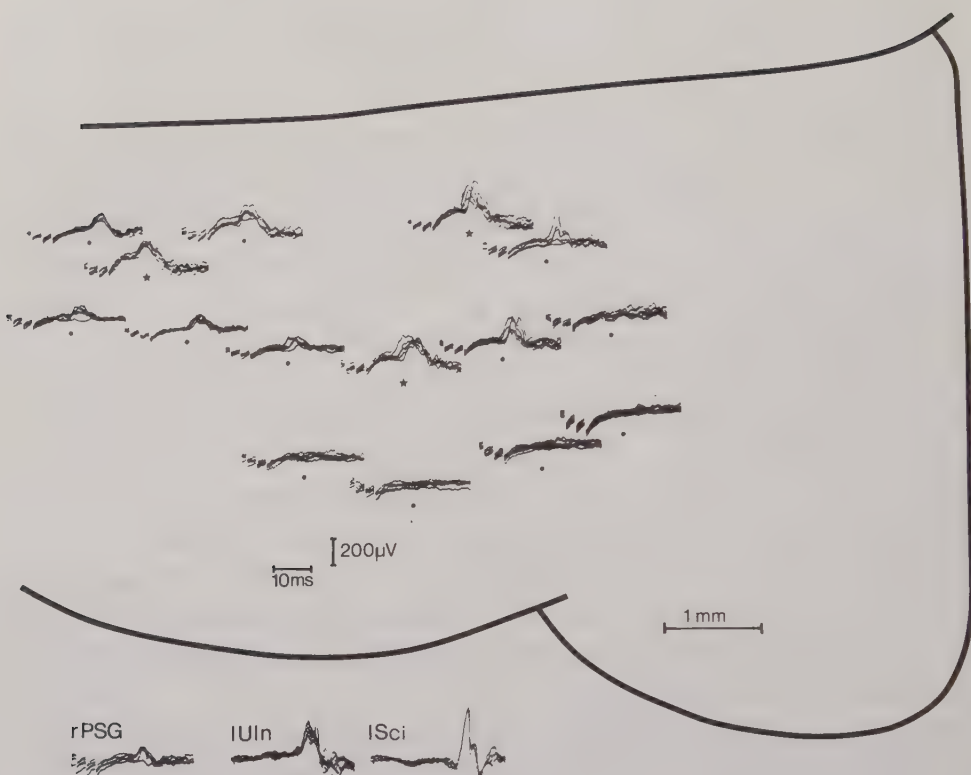


Fig. 7. Climbing fibre projection from the right anterior sigmoid gyrus to the left d1 zone in lobule IV. Inlaid records are responses in the d1 zone on intracortical stimulation at a depth of 2mm at the sites indicated with dots and stars, which also indicate latency of 15ms. Stimulation strength 0.5mA. Lower row of records: responses in the d1 zone on stimulation of the optimal site in the right posterior sigmoid gyrus (rPSG), left ulnar (Uln) and sciatic (Sci) nerves. Pentobarbitone anaesthesia.

DISCUSSION

The results of the present study demonstrate a zonal pattern in the climbing fibre projection to the cerebellar anterior lobe from the cerebral cortex. This zonal pattern is related to the sagittal zones which can be identified from the peripheral climbing fibre input.

Fig. 8 is a summary diagram showing the cortical areas projecting to each zone in lobule V. Dense hatching indicates areas from where responses were evoked in more than 80% of the experiments. Sparse hatching indicates areas from where responses were evoked in at least 40% of the experiments. In addition to these projections, responses were occasionally evoked in some of the zones from areas not hatched in Fig. 8 (cf. Fig. 3). These responses were recorded mainly under chloralose anaesthesia and often had higher thresholds and lower amplitudes than the responses which have been considered for Fig. 8.

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The use of dense hatching in the long-latency area in the ASG and sparse hatching in the SI is somewhat tentative. Although it was impossible, in some cases, to identify the minimum threshold sites for evoking long-latency responses from the ASG and to obtain a plateau on the latency curves of these responses, long-latency responses were evoked from the lateral ASG in almost all experiments. Therefore, it seems justified to indicate this area with dense hatching. Stimulation of the SI less frequently evoked climbing fibre responses at moderate stimulus strengths. Hence, this area is indicated with sparse hatching.

In addition, the medial PSG area which projects to the c2 and d1 zones in the rostral part of lobule V is, for the sake of clarity, not shown.

The predominant projection originates in the pericruciate cortex. From sensory and parietal cortical areas considerably weaker projections were generally observed. The zones receive characteristically different inputs. The most conspicuous features are:

The a and b zones receive almost equally strong PSG inputs from both sides.

The x, c1 and c3 zones, which have similar, ipsilateral peripheral inputs, receive contralateral cortical inputs only, mainly from the PSG. Two separate areas project to these zones, one lateral, extending rostrally into the lateral part of the ASG, to the forelimb parts and

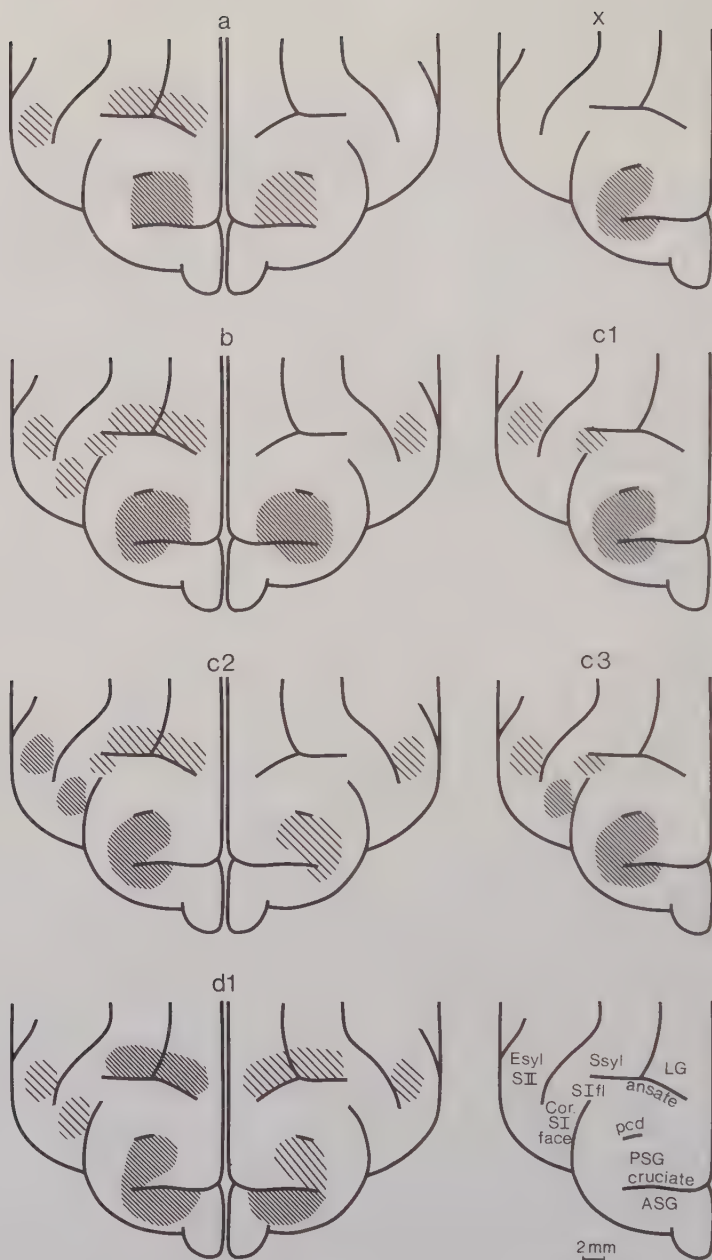


Fig. 8. Summary diagram of cerebral cortical areas from which climbing fibre responses could be evoked in the respective zones in more than 80% of the experiments (dense hatching) or in at least 40% of the experiments (sparse hatching). Abbreviations as in Fig. 2.

one medial to the hindlimb parts.

The PSG projection to the c2 zone resembles that to the x, c1 and c3 zones but is bilateral. There are also projections from the second somatosensory area (SII), the coronal gyrus and the parietal cortex.

The d1 zone contrasts with the other zones by receiving a strong projection from the parietal cortex and a short-latency projection from a large area in the ASG.

A comparison with the cytoarchitectonic map of Hassler and Muhs-Clement (1964) reveals that the major part of the short-latency (PSG) area belongs to area 4 γ . A projection from the group I receiving area 3a (Oscarsson and Rosén 1963, 1966; Landgren and Silfvenius 1969) can not be excluded. The PSG area projecting to the hindlimb zones (Fig. 6A) also seems to correspond to the dorsal hindlimb group I locus of Landgren and Silfvenius (1969).

Long-latency responses were evoked in several zones on stimulation of an area in the lateral ASG (Figs. 5 and 6), which seems to lie within area 4 γ . In the d1 zone, short-latency responses were elicited from an area which extended further medially and, hence, might include part of area 6a β . However, since histological analysis was not made, the relationship between the projecting areas and the cytoarchitecture remains uncertain.

The tendency for two minimum threshold areas to occur within the short-latency area projecting to the forelimb zones might be related to the finding that two spatially separate representations exist for the distal forelimb muscles in area 4 γ (Pappas and Strick 1981). Although located slightly more laterally, these two "digit zones" had approximately the same position as the two minimum threshold areas in the present study, i.e., the caudal area, midway between the lateral tip of the cruciate sulcus and the postcruciate dimple, and the rostral area, close to the tip of the cruciate sulcus (Fig. 6A). Pappas and Strick suggest that the double representation may reflect the existence of two motor control systems dealing with different components of motor behaviour. If so, it might be important that both these motor control systems project also to the cerebellum (see below), as suggested by the present findings.

Interestingly, the minimum threshold sites in the PSG for the b zone

(Fig. 6B) seem to be located in the area which sends corticospinal fibres both ipsilaterally and contralaterally (Armand and Kuypers 1980) and fibres with collaterals to both the cervical and lumbar enlargements (Hayes and Rustioni 1981). The efferent projection from this area thus resembles the afferent projection to the b zone, bilateral and with some overlap of the forelimb and hindlimb projections.

In general, the present results have confirmed those of previous studies on the cortico-olivo-cerebellar projection (Provini et al. 1968; Miller et al. 1969a; Allen et al. 1974a,b; Miles and Wiesendanger 1975a,b; Sasaki et al. 1975; Oka et al. 1976,1979; Rowe 1977a). Summarising these reports, there is a somatotopically organised climbing fibre input to nearly all Purkinje cells in the anterior lobe from the PSG. A substantial proportion of the cells receive also an input from the SI and SII. Most Purkinje cells receive converging climbing fibre inputs from peripheral nerves and somatotopically corresponding parts of the sensorimotor cortex. There is also a projection from the ASG which does not seem to be somatotopically organised. Long-latency responses can be evoked on stimulation of the parietal cortex. The responses from the SI, SII and parietal cortex are mediated through separate cortico-olivary paths, since ablation of the pericruciate cortex did not abolish these responses (Sasaki et al. 1975; Rowe 1977a).

The results of the present and previous studies suggest the existence of a multitude of cortico-olivo-cerebellar pathways, originating in different areas of the cerebral cortex and terminating in separate cerebellar zones (see above, Fig. 8). The difference in thresholds for evoking responses, as well as in response latencies, between some of the zones on stimulation of a single cortical site indicates that cortico-olivo-cerebellar pathways originating in one cortical area, but terminating in different zones, can have different synaptic organisations.

In the experiment illustrated in Fig. 2, for example, stimulation of the PSG evoked responses in all zones except the c2 zone. However, in other experiments, a projection from the PSG to the c2 zone was observed. Its absence in that particular experiment might be explained by a low excitability of the olivary neurones projecting to the c2 zone. This is, however, rather unlikely since responses were evoked in the c2 zone on stimulation of peripheral nerves and the contralateral

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SII. It seems more likely that the pathway from the PSG to c2 has a different synaptic organisation from the pathways to the other zones and that, in the illustrated experiment, the transmission through this pathway was suppressed.

The pathways mediating the cortically induced climbing fibre responses are largely unknown. Anatomical investigations have indicated a direct, bilateral cortico-olivary path (Walberg 1956; Sousa-Pinto 1969; Sousa-Pinto and Brodal 1969; Bishop et al. 1976; Brown et al. 1977; Berkley and Worden 1978). These results have, however, been questioned (Saint-Cyr and Courville 1980). Thus, the climbing fibre responses observed in the present, as well as in previous studies, might be mediated through indirect cortico-olivary paths. The relay nuclei, with one exception, have not been identified, but the inferior olive receives a descending input from several structures. These projections have recently been reviewed in detail (Brodal and Kawamura 1980, Cintas et al. 1980; Martin et al. 1980; Saint-Cyr and Courville 1980).

Physiological studies have demonstrated that climbing fibre responses evoked in both the vermis and pars intermedia on sensorimotor cortex stimulation are mediated by slowly conducting fibres in the pyramidal tract (Cervetto et al. 1969; Kitai et al. 1969). Despite the rather slow conduction velocity, the response latency on pyramidal tract stimulation seems to be sufficiently long to additionally include a pre-olivary relay. Interestingly, the conduction velocity of pyramidal tract fibres mediating responses to the forelimb area of the cerebellum was faster (mean 10.0 m/s) than the velocity of the fibres mediating a response to the hindlimb area (mean 8.4 m/s) (Kitai et al. 1969). This is in agreement with the findings in the present study, where responses from the medial PSG in the hindlimb zones usually had slightly longer latencies (mean difference 1.5 ms) than those from the lateral PSG in forelimb zones.

The only well-established relay in a cortico-olivary path is the parvocellular part of the red nucleus (Oka and Jinnai 1978a,b; Oka et al. 1979). This has been shown to mediate parietal-evoked climbing fibre responses to the d1 zone (cf. Miller et al. 1969b; Jeneskog 1974a,b, 1981). Whether the responses in the other zones also are mediated through the parvocellular red nucleus is uncertain.

A general finding of both the present and previous studies is that

stimulation of one cortical site evoked a response not only in a large part of one zone but in several zones. A response at one cerebellar recording site, or in a single Purkinje cell, could also be evoked from many stimulation sites within one cortical area, as well as from several separate areas. This divergence and convergence must be considered when discussing the functional role of the cortico-olivo-cerebellar projection.

The inferior olive has been suggested to function as a comparator of descending and ascending information (Miller and Oscarsson 1970; Oscarsson 1980). Each sagittal zone, and its associated cerebellar or vestibular nucleus, probably constitute a functional unit of the cerebellum, and is concerned with controlling a particular motor mechanism (Oscarsson 1980). Each zone would then receive information which is relevant to this motor function.

The striking parallelism in the distribution pattern of the climbing fibre responses evoked in the cerebellar zones (with the exception of c2) on stimulation of peripheral nerves and the corresponding areas in the sensorimotor cortex reveals that each part of the inferior olive receives convergent inputs from certain segments of the spinal cord and the corresponding part of the motor cortex. This is consistent with, and is, indeed, a prerequisite for, the comparator hypothesis.

If stimulation of a particular cortical site evokes responses in several zones, it would imply that this stimulation also affects each of the motor mechanisms controlled by the activated zones.

Indeed, it has been shown that, in addition to exciting motoneurons in a topographical manner (Livingston and Phillips 1957; Asanuma and Sakata 1967; Asanuma et al. 1968; Nieuoullon and Rispal-Padel 1976; Pappas and Strick 1981), stimulation of the sensorimotor cortex produces many other effects. For example, stimulation of the area which activates distal forelimb muscles via the pyramidal tract, also activates the proximal forelimb muscles through extrapyramidal pathways (Asanuma et al. 1981). This effect is probably part of a postural adjustment (Gahéry and Massion 1981). Furthermore, stimulation of the sensorimotor cortex facilitates and/or depresses the transmission through different spinal reflex arcs (Lundberg and Voorhoeve 1962; Hongo and Jankowska 1967), through jaw reflex arcs (Olsson and Landgren 1980), through ascending spinal tracts (Magni and Oscarsson 1961;

Lundberg et al. 1963; Hongo et al. 1967; Hongo and Okada 1967), and through the dorsal funiculus nuclei (Jabbur and Towe 1961; Andersen et al. 1964d,e; Gordon and Jukes 1964; Levitt et al. 1964). In addition, depolarisation of presynaptic fibre terminals in the spinal cord (Carpenter et al. 1963; Andersen et al. 1962, 1964a; Abdelmouméne et al. 1970) and in the dorsal funiculus nuclei (Andersen et al. 1964b,c) is also produced by stimulation of this cortical area.

Thus, a large number of interneurone pools, participating in different mechanisms, are activated from the sensorimotor cortex. If the cerebellar zones participate in the control of these mechanisms each zone should receive information about the activation of its particular interneurone pool. Hence, the divergence to several zones from those cortical sites which activate functionally separate interneurone pools would be expected.

Similarly, the convergence from several stimulation sites to one cerebellar recording site, or to a single Purkinje cell, could be compared to the convergent effects from more than one cortical site, or area, onto particular interneurone pools. Many of the effects on sensorimotor cortex stimulation mentioned above were elicited from a large area rather than from only one site or from several separate areas. Some of the effects were also bilateral.

Thus, more than one cortical area can be concerned with the regulation of a particular function and, consistent with the comparator hypothesis, can also converge onto a certain cerebellar zone.

The cortically induced inhibition of ascending spinal tracts, mentioned above, also applies to the spino-olivo-cerebellar pathways (Leicht et al. 1972, 1973; Fennel and Rowe 1973; Rowe 1977b). It was often shown in these studies that both climbing fibre excitation of a Purkinje cell and inhibition of its response to a peripheral stimulus were evoked from the same cerebral cortical stimulation site. Usually, the inhibition was achieved with a lower stimulus strength than the excitation. At least part of the inhibition occurred at preolivary levels. In some, but far from all, Purkinje cells, the cortically induced inhibition was somatotopically organised.

Thus, the cerebral cortex can inhibit the peripheral climbing fibre input to the cerebellum. This might be a mechanism by which the cerebral cortex cancels peripheral input which is expected

in connection with a movement. Unexpected peripheral input, however, brought about by an error in the executed movement, might be transmitted to the cerebellum. In such a case, the comparator function would be exerted through a comparison of the cortical inhibitory and ascending excitatory inputs to the olive.

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